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(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFAtppaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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A METHOD for extracting quantitative information relating to an influence on a cellular response

FIELD OF INVENTION

The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

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BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi et al.1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano et al.1995)].

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Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al. 1995)] nucleus [(Khalil et al. 1992)], cytoskeleton [(Blobe et al. 1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al. 1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al. 1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schmidt et al. 1997]) and of PKCγ and PKC ε([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

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Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

DISCLOSURE OF THE INVENTION

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The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

The cells

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In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

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A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

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such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

Apparatus

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The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

15 Quantitation of the influence

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The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

Nucleic acid constructs

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- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto,
 e.g. an isoform, or a splice variant or a homologue from another species.

Screening program

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The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

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detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

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the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
 (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
 - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²⁺ and K⁺, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

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- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.
- The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

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The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it 5 localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does 10 not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

Developing an image-based assay technique

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The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

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- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
 can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

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necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

10 Example: Developing a Quantitative assay for GLUT4 Translocation

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GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

10 **Definitions**:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie *et al.*1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish *Aequorea victoria* and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from *Aequorea* Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

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The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant" ,when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

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The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The 15 cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived from a mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hy-20 bridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, 25 bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

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GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC α -GFP, PKC γ -GFP, and PKC ϵ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

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The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

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termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

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ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP], N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

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Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal ($t_{1/2max}$) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2max}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

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Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

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Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 $^{\circ}\text{C}$.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

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Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM
 F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- 30 b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

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The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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EXAMPLE 1

Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the $G_{\rm S}$ or $G_{\rm I}$ class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4) ,

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

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The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml⁻¹, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) andPKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml⁻¹ and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

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and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
 - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
 - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
 - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
 - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

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Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
- 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca²⁺-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- 25 CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
 - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

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The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

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distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G₁ protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]_i (Fig. 3H).

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Fusion protein translocation correlated with [cAMP],

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKC α (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCGCCATgAgTAAAggAgAAGAACTT-10 TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-XhoI casette as described in example 1.

15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metal-lothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC α -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 µg Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC α -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 µg Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 µg penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

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CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKC α -F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 15 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
 - 4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
- 5. The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

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- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
 - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:

5'ERK1: TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCggCTCCgggggggCgggg (SEQ ID NO:7),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGATT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+Xhol. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+Xhol. The two pairs of digested PCR products are subsequently ligated with a HindIII+Xhol digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

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b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4:

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Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5:

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10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc651, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc651. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

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Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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EXAMPLE 7:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
- b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

Example 9:

30 Probes for detection of Jnk1 redistribution.

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Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylylcyclase/cGMP signal.

- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cytoplasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

Example 11:

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- 20 Probes for detection of IkappaB kinase redistribution.
 - Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.
 - a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc651, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc651. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-IkappaB-kinase probe and/or the IkappaB-kinase-EGFP probe should achieve a more
cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

Example 12:

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Probes for detection of CDK2 redistribution.

- Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.
- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
 - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

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The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.
 - a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-
- bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

30 Example 14:

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution from cytoplasmic to membrane-associated within seconds in response to activation of the T cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

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- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

Example 16:

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Probes for detection of protein-tyrosine phosphatase redistribution.

- 20 Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

Example 17:

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Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
 - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

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The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
 &79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.

- a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.

- b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; Gen-
- Bank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA. Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

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57

SEQUENCE LISTING

| 5 | (1) GENERAL INFORMATION |
|----|---|
| | (i) APPLICANT: NovoNordisk, BioImage |
| 10 | (ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging |
| | (iii) NUMBER OF SEQUENCES: 143 |
| 15 | (iv) CORRESPONDENCE ADDRESS:(A) ADDRESSEE: NovoNordisk, BioImage(B) STREET: Mørkhøjbygade 28(C) CITY: Søborg |
| 20 | (D) STATE: DK (E) COUNTRY: DENMARK (F) ZIP: 2860 |
| 25 | (v) COMPUTER READABLE FORM:(A) MEDIUM TYPE: Diskette(B) COMPUTER: IBM Compatible |
| | (C) OPERATING SYSTEM: DOS (D) SOFTWARE: FastSEQ for Windows Version 2.0 |
| 30 | <pre>(viii) ATTORNEY/AGENT INFORMATION: (A) NAME: , PV&P R (B) REGISTRATION NUMBER: (C) REFERENCE/DOCKET NUMBER:</pre> |
| 35 | (2) INFORMATION FOR SEQ ID NO:1: |
| | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 53 base pairs |
| 40 | (B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear |
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| | TTGGACACAA GCTTTGGACA CGGCGCGCCA TGAGTAAAGG AGAAGAACTT TTC 53 |
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| 55 | <pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre> |
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59

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| 35 · | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
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WO 98/45704

| | | PCT/DK98/00145 |
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| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14: | |
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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

| WO 98/45704 | PCT/DK98/0014 |
|-------------|---------------|
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(D) TOPOLOGY: linear

| 5 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15: | |
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| 10 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 15 | (b) TOPOLOGI: IIIIEAI | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16: | |
| 20 | ATGGATCCTC AGGACTCCAT CTCTTCTTG | 29 |
| 20 | (2) INFORMATION FOR SEQ ID NO:17: | |
| 25 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 30 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: | |
| | GTCTCGAGCC ATCATGAGCA GAAGCAAG | 28 |
| 35 | (2) INFORMATION FOR SEQ ID NO:18:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs | |
| | (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| 40 | (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18: | |
| 45 | GTGGATCCCA CTGCTGCACC TGTGCTA | 27 |
| | (2) INFORMATION FOR SEQ ID NO:19: | |
| 50 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 55 | | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19: | |

| | GIGGATCCTC ACTGCTGCAC CTGTGCTA | 28 |
|----|---|----|
| 5 | (2) INFORMATION FOR SEQ ID NO:20: | 20 |
| | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 40 base pairs | |
| | (B) TYPE: nucleic acid | |
| 10 | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (2) Torologi: Timear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20: | |
| 15 | CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC | 40 |
| | (2) INFORMATION FOR SEQ ID NO:21: | |
| 20 | (i) SEQUENCE CHARACTERISTICS: | |
| 20 | (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid | |
| | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| 25 | | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21: | |
| | CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC | 32 |
| 30 | (2) INFORMATION FOR SEQ ID NO:22: | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| | (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid | |
| 35 | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| | (vi) ORIGINAL SOURCE: | |
| 40 | (A) ORGANISM: p85-top-C | |
| 40 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22: | |
| | GGGAGATCTA TGAGTGCTGA GGGGTACCAG | 30 |
| 45 | (2) INFORMATION FOR SEQ ID NO:23: | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| | (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid | |
| 50 | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| 55 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23: | |
| 30 | GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC | |
| | - THE COURT ISCIBIGUAT ATAC | 34 |
| | | 62 |
| | | |

| | (2) INFORMATION FOR SEQ ID NO:24: | |
|----------|--|----|
| 5 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 10 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: | |
| | GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC | 33 |
| 15 | (2) INFORMATION FOR SEQ ID NO:25: | |
| 20 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 25 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: | |
| | GTGGTACCCA TGACATGCTT GAGCAACGCA C | 31 |
| | (2) INFORMATION FOR SEQ ID NO:26: | |
| 30 35 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: | |
| 40 | GTGGTACCTT ATGACATGCT TGAGCAACGC AC | 32 |
| | (2) INFORMATION FOR SEQ ID NO:27: | |
| 45 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 50 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: | |
| | GTGAATTCGT CAATGGAGCT GGAAAACATC G | 31 |
| 55 | (2) INFORMATION FOR SEQ ID NO:28: | |
| -• | (i) SEQUENCE CHARACTERISTICS: | |

| | | PCT/DK98/00145 |
|----|--|----------------|
| | 64 | |
| | (A) LENGTH: 30 base pairs(B) TYPE: nucleic acid | |
| | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| 5 | Tancar | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: | |
| 10 | GTGGATCCCT GCTGCTTCCG GTGGAGTTCG | 30 |
| | (2) INFORMATION FOR SEQ ID NO:29: | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| 45 | (A) LENGTH: 31 base pairs | |
| 15 | (B) TYPE: nucleic acid | |
| | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| 20 | (XI) SEQUENCE DECENSA- | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: | |
| | GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G | 2.1 |
| 25 | (2) INFORMATION FOR SEQ ID NO:30: | 31 |
| 25 | | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| | (A) LENGTH: 32 base pairs | |
| | (B) TYPE: nucleic acid | |
| 30 | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (b) TopoLogY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: | |
| 35 | | |
| | GTAGATCTAC CATGGCGGGC TGGATCCAGG CC | 32 |
| | (2) INFORMATION FOR SEQ ID NO:31: | |
| 40 | (i) SEQUENCE CHARACTERISTICS: | |
| 40 | (A) LENGTH: 31 base pairs | |
| | (B) TYPE: nucleic acid | |
| | (C) STRANDEDNESS: single | |
| 45 | (D) TOPOLOGY: linear | |
| 45 | (- ') - mm- | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31: | |
| | GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A | 31 |
| 50 | (2) INFORMATION FOR SEQ ID NO:32: | 31 |
| | (i) SEQUENCE CHARACTERISTICS: | |
| | (A) LENGTH: 31 base pairs | |
| 55 | (B) TYPE: nucleic acid | |
| JU | (C) STRANDEDARGE | |

64

(C) STRANDEDNESS: single (D) TOPOLOGY: linear

65

| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32: | |
|----|--|----|
| 5 | GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G | 31 |
| | (2) INFORMATION FOR SEQ ID NO:33: | |
| 10 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 15 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33: | |
| | | |
| | GTGAATTCAA CCATGGACAA TATGTCTATT ACG | 33 |
| 20 | (2) INFORMATION FOR SEQ ID NO:34: | |
| 25 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 30 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: | |
| | GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C | 31 |
| | (2) INFORMATION FOR SEQ ID NO:35: | |
| 35 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single | |
| 40 | (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: | |
| | GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC | 32 |
| 45 | (2) INFORMATION FOR SEQ ID NO:36: | |
| 50 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 55 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36: | |

GTCTCGAGGC ACCATGAGCG ACGTGGC

- (2) INFORMATION FOR SEQ ID NO:37:
- 5 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TGGGATCCGA GGCCGTGCTG CTGGCCG

15

- (2) INFORMATION FOR SEQ ID NO:38:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1896 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- 25 (ix) FEATURE:

10

30

40

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...1891
- (D) OTHER INFORMATION:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

10 15

GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC
Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35
40
45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr

50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys

70

75

80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
55 90 95

| | | | | | | 01 | | | | | |
|----|--|--|-------------------|--|--|----|---|---|---|---|-----|
| | | | TTC Phe | | | | | | | | 336 |
| 5 | | | GGC Gly | | | | | | | _ | 384 |
| 10 | | | GAG Glu | | | | | | | | 432 |
| 15 | | | CAC His | | | | | | | | 480 |
| 20 | | | AAC Asn 165 | | | | _ | _ | _ | | 528 |
| 20 | | | GAC Asp | | | | | | | | 576 |
| 25 | | | CCC Pro | | | | | | | | 624 |
| 30 | | | AAC Asn | | | | | | | | 672 |
| 35 | | | GGG Gly | | | | | | | | 720 |
| 40 | | | CGA Arg 245 | | | | | | | _ | 768 |
| 40 | | | GGC Gly | | | | | | | | 816 |
| 45 | | | CCG Pro | | | | | | | | 864 |
| 50 | | | CGC Arg | | | | | | _ | _ | 912 |
| 55 | | | AGC Ser | | | | | | | _ | 960 |

| | 68 |
|----|--|
| | GCC ATC AAG AAG ATC AGC CCC TTC GAA CAT CAG ACC TAC TGC CAG CGC Ala lle Lys Lys lle Ser Pro Phe Glu His Gln Thr Tyr Cys Gln Arg 325 330 335 |
| | Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe Arg His Glu Asn Val |
| 10 | 355 360 Ser Thr Leu Glu Ala Met Arg |
| 15 | 375 380 The Asp Leu Tyr Lys Leu |
| 20 | CTG AAA AGC CAG CAG CTG AGC AAT GAC CAT ATC TGC TAC TTC CTC TAC Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile Cys Tyr Phe Leu Tyr 395 CAG ATC CTG CGG CGG CTG No. |
| 25 | CAG ATC CTG CGG GGC CTC AAG TAC ATC CAC TCC GCC AAC GTG CTC CAC Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn Val Leu His 405 410 415 |
| | CGA GAT CTA AAG CCC TCC AAC CTG CTC AGC AAC ACC ACC TGC GAC CTT 1296 Arg Asp Leu Lys Pro Ser Asn Leu Leu Ser Asn Thr Thr Cys Asp Leu 420 425 430 |
| 30 | AAG ATT TGT GAT TTC GGC CTG GCC CGG ATT GCC GAT CCT GAG CAT GAC Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala Asp Pro Glu His Asp 435 440 445 |
| 35 | CAC ACC GGC TTC CTG ACG GAG TAT GTG GCT ACG CGC TGG TAC CGG GCC His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp Tyr Arg Ala 450 450 460 |
| 40 | CCA GAG ATC ATG CTG AAC TCC AAG GGC TAT ACC AAG TCC ATC GAC ATC Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser Ile Asp Ile 475 480 |
| 45 | TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC TCT AAC CGG CCC ATC 1488 Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn Arg Pro Ile 490 495 |
| 43 | TTC CCT GGC AAG CAC TAC CTG GAT CAG CTC AAC CAC ATT CTG GGC ATC Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile Leu Gly Ile 500 500 510 |
| 50 | CTG GGC TCC CCA TCC CAG GAG GAC CTG AAT TGT ATC ATC AAC ATG AAG Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile Asn Met Lys 515 520 525 |
| 55 | GCC CGA AAC TAC CTA CAG TCT CTG CCC TCC AAG ACC AAG GTG GCT TGG Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys Thr Lys Val Ala Trp 530 535 540 |

| | 69 | | | | | | | | | | | | | | | | |
|----|--|------------|-----------|-------------------|-----------|-----------|------------|-----------|------------|-----------|-----------|------------|-----------|------------|-----------|-----------|------|
| | | | | TTC Phe | | | | | | | | | | | | | 1680 |
| 5 | | | | ACC Thr | | | | | | | | | | | | | 1728 |
| 10 | | | | CCC Pro 580 | | | | | | | | | | | | | 1776 |
| 15 | | | | GAG Glu | | | | | | | | | | | | | 1824 |
| 20 | | | | CTG Leu | | | | | | | | | | | | | 1872 |
| 20 | | | | CTG Leu | | _ | | CTAG | | | | | | | | | 1896 |
| 25 | (2) INFORMATION FOR SEQ ID NO:39: | | | | | | | | | | | | | | | | |
| 30 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 631 amino acids(B) TYPE: amino acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | | | | | | | | | | | | | | | | |
| 35 | <pre>(ii) MOLECULE TYPE: protein 5 (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:</pre> | | | | | | | | | | | | | | | | |
| | 14-4 | | | | | | | | | | | | 17-1 | Dwa | T10 | Lon | |
| 40 | 1 | | | Lys | 5 | | | | | 10 | _ | | | | 15 | | |
| | | | | 20 Gly | _ | - | | | 25 | | - | | | 30 | | | - |
| 45 | Cys | | 35 Thr | Gly | Lys | Leu | | 40 Val | Pro | Trp | Pro | | 45 Leu | Val | Thr | Thr | |
| | Leu 65 | 50 Thr | Tyr | Gly | Val | Gln 70 | 55 Cys | Phe | Ser | Arg | Tyr 75 | 60 Pro | Asp | His | Met | Lys 80 | |
| 50 | | His | Asp | Phe | Phe 85 | | Ser | Ala | Met | Pro 90 | | Gly | Tyr | Val | Gln 95 | | |
| | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | | Tyr | Lys | Thr | Arg 110 | Ala | Glu | |
| | | - | 115 | Glu | | | | 120 | | | | | 125 | | | | |
| 55 | Ile | Asp 130 | Phe | Lys | Glu | Asp | Gly 135 | Asn | Ile | Leu | Gly | His 140 | Lys | Leu | Glu | Tyr | |

| | | | | | | | | 70 | | | | | | |
|----|-----------------------|---------------|--------------|------------|------------|------------|--------------|-------|-------------|-------------|--------------|------------|------------|------------|
| | Asn T | yr Asr | ı Ser | His A | sn V | al T | yr Il | e Met | : Ala | Asp | Lys | Gln | Lvs | . Asn |
| | Gly I | le Lys | . Val | 1 Asn P | 50 he L | vs I | le Ar | a Wie | 155 | 71- | ~ . | | | 160 |
| 5 | Val G | ln Lou | . הוה | 165 | | | | 170 |) ASII | 116 | GIU | Asp | Gly 175 | Ser |
| | | ln Leu | | | | | | | | | | | | |
| | | al Leu 195 | | | | | | | | | | Ser | | |
| 10 | | ys Asp 10 | | | | | | | | | Leu | | | |
| | | hr Ala | | | | | | | | Glu | | | | |
| | Gly L | eu Arg | Ser A | Arg Al | la Gl | n Al | a Ser | Asn | Ser | Thr | Met | Ala | Ala | 240 Ala |
| 15 | Ala A | | | | | | y Glu | Pro | | | | | | |
| | Gly Pı | 0 Gly 275 | Val F | ro Gl | y Gl | u Va | l Glu | Met | Val : | Lys (| Gly | 270 Gln | Pro | Phe |
| 20 | Asp Va | | | | r Th | r Gl | | | | | | | | |
| | Tyr Gl | | | er Se | r Ala | | | | | | | | | |
| | Ala Il | | | | | | | | | | | | | |
| 25 | Thr Le | | | | | | | | | | | | | |
| | Ile Gl | | | | | | | | | | | | | |
| | Asp Va | | | | | | | | | | | | | |
| 30 | | | | | | | | | | | | | | |
| | Leu Ly: | | | | | | | | | | | | | |
| | Gln Ile | | | | | | | | | | | | | |
| 35 | Arg Asp | Leu I | ys Pr 120 | o Ser | Asn | Leu | Leu 425 | Ser A | Asn T | hr T | hr C | ys A | 15 sp I | Leu |
| | Lys Ile | Cys <i>I</i> | Asp Ph | e Gly | Leu | Ala 440 | Arg | Ile A | Ala A | sp Pi | 4. .co G. | 30 lu H | is A | asp |
| 40 | His Thr 450 | Gly F | he Le | u Thr | Glu 455 | Tyr | Val . | Ala T | hr A | 44 cg Ti | 15 op T | yr A | rg A | la |
| | Pro Glu 465 | Ile M | let Le | u Asn | Ser | Lys | Gly | Tyr T | 46 hr Ly | 50 ⁄s S∈ | r I | le A | sp I | le |
| | Trp Ser | | | | | | | | | | | | | |
| 45 | Phe Pro | Gly L | ys Hi | | | | | | | | | | | |
| | Leu Gly | | | | | | | | | | | | | |
| 50 | Ala Arg 530 | | | | | | | | | | | | | |
| 50 | 530 Ala Lys 545 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| 55 | Arg Met | | | | | | | | | | | | | |
| 55 | Leu Ala | His Pr | TO Tyr | Leu | Glu (| Gln ' | Tyr T 585 | yr As | sp Pr | O Th | r As 59 | p G1 0 | u Pi | 0 |

| | | • | | | | | | | | | | | | | | | |
|----|-----------------|------------|-------------------|------------------------------|---------------------|----------------------|-------------|----------------------|-------|--------|--------|------------|-------------------|-----|-----|-----|-----|
| | Val . | Ala | Glu 595 | Glu | Pro | Phe | Thr | Phe 600 | Ala | Met | Glu | Leu | Asp 605 | Asp | Leu | Pro | |
| | Lys | Glu 610 | | Leu | Lys | Glu | Leu 615 | | Phe | Gln | Glu | Thr 620 | Ala | Arg | Phe | Gln | |
| 5 | Pro 625 | | Val | Leu | Glu | Ala 630 | | | | | | | | | | | |
| | | | (2) | INF | ORMA | TION | FOF | SEC | DI | NO : 4 | 0: | | | | | | |
| 10 | | (i | (A) (B) (C) | QUEN LENG TYPE STRA | TH: : nu NDED | 1818 clei NESS | bas c ac | e pa :id .ngle | irs | | | | | | | | |
| 15 | | ٠. | | OLEC EATU | | TYPE | : cI | NA | | | | | | | | | |
| 20 | | | (B) | NAM LOC | ATIC | N: 1 | 1 | 815 | equer | ice | | | | | | | |
| | | (х | (i) S | EQUE | ENCE | DESC | RIPT | ION: | SEÇ |) ID | NO : 4 | 0: | | | | | |
| 25 | ATG Met 1 | | | | | | | | | | | | | | | | 48 |
| 30 | GTC Val | | | | | | | | | | | | | | | | 96 |
| 35 | GAG Glu | | | | | | | | | | | | CTG Leu 45 | | | | 144 |
| 40 | | | | | | | | | | | | | CTC Leu | | | | 192 |
| 40 | | | | | | | | | | | | | GAC Asp | | | | 240 |
| 45 | | | | | | | | | | | | | TAC Tyr | | | | 288 |
| 50 | | | | | | | | | | | | | ACC Thr | | | _ | 336 |
| 55 | | | | | | | | | | | | | GAG Glu 125 | | | | 384 |

| | | | | | | | | | | | | | 72 | | | | | | | | | | |
|----|-------------------|-----------|--------------|-------------------|--------------------|--------------------|------------|--------------|----------------|-------------------|-------------------|------------|-------------------|-------------------|----------------|--------------|----------------|-------------------|----------------|----------------|-------------------|--------|------|
| | | | 13 | Ò | rc A ne L | | | | 13 | у А. 5 | 211 | тте | . re | u G | ТУ | His 140 | Ly | s L | eu | Gl | и Ту | r | 432 |
| 5 | 14 | 45 | • | | C A | | | 150 | va. | 1 1) | / <u>F</u> | 116 | ме | t A | 1a 55 | Asp | Ly | s Gi | ln | Lys | 3 As: | n 0 | 480 |
| 10 | | - | | • | G G: | 1 | 65 | 1110 | Dy s | , 11 | | arg | 17 | s As 0 | sn | Ile | Glı | ı As | gp | Gly 175 | 7 Se | r | 528 |
| 15 | | | | | C GC u Al 18 | 0 | -p | ***** | 171 | . 61 | 11 (| 185 | Ası | ı Th | ır . | Pro | Ilε | Gl 19 | y 2 0 | Asp | Gly | 7 | 576 |
| 20 | | | | 195 | | | | nsp | ASII | 200 | 0 | yr | Let | ı Se | r ' | Thr | Gln 205 | Se | r A | \la | Leu | ı | 624 |
| | | 2 | 210 | | C CC | - 11. | ,,,, | JIU | 215 | Arç | JA | ap | His | Me | t V | /al 220 | Leu | Le | u G | lu | Phe | | 672 |
| 25 | 225 | 5 | | | GC6 | - 0. | 2 | 30 | 1111 | neu | נט | ΙY. | Met | 23! | р G 5 | lu | Leu | Туз | r L | ys | Ser 240 | | 720 |
| 30 | GG# Gly | A C | TC eu | AGA Arg | TC: | CG Ar 24 | . | TA / | ACC Thr | ATG Met | G(| ıa A | GCG Ala 250 | GC0 Ala | G G | CG (| GCG Ala | GCC Ala | G | GC ly 55 | CCG Pro | | 768 |
| 35 | GAG Glu | A M | TG et | GTC Val | CGC Arg 260 | O.L. | G C Y G | AG (| GTG /al | TTC Phe | G# As 26 | gp \ | GTG Val | GGC Gly | G C | CG (| CGC Arg | TAC Tyr 270 | T] | CT . | AAT Asn | | 816 |
| 40 | CTC Leu | Se | | TAC Tyr 275 | ATC | GG/ Gly | A G | AA G | ту | GCC Ala 280 | ТА | AC G | GC Bly | ATG Met | G: Va | al C | GT Ys 85 | TCT Ser | G(| CT ' | TAT Tyr | | 864 |
| | GAT Asp | AA As | AT (sn 1 | CTC Leu | AAC Asn | AA <i>I</i> Lys | A GT | 1 T | GA rg 95 | GTT Val | GC Al | T A a I | TC le | AAG Lys | AA Ly 30 | s I | TC . | AGT Ser | CC | T : | rrr Phe | | 912 |
| 45 | GAG Glu 305 | CA | .C (| AG In | ACC Thr | ТАС Туг | Су 31 | 3 0 | AG 1 | AGA Arg | AC Th | c c | eu . | AGA Arg 315 | GA Gl | AG A .u I | TA A | AAA Lys | AT Il | e I | CTA Leu 120 | | 960 |
| 50 | CTG Leu | CG Ar | C I | TC he | AGA Arg | CAT His 325 | 0.1 | G A | AC A | ATC [le | AT Il | e G | GC / ly : | ATC Ile | AA As | T G. | AC A | ATC [le | AT Il 33 | e A | :GG .rg | 1 | .008 |
| 55 | GCA Ala | CC. Pr | A A | | ATT Ile 340 | GAG Glu | CA Gl: | G A: n Me | rg A | ys . | GA: Asp 345 | o Va | TA : | FAT Fyr | AT. | AG: | al G | CAG Sln | GA Asj | c c | TC eu | 1 | 056 |

| | | | | | | 13 | | | | | |
|----|--|--|-------------------|---|---|----|---|---|---|---|------|
| | | | CTT Leu | | | | | | | | 1104 |
| 5 | | | TAT Tyr | | _ | _ | | _ | | | 1152 |
| 10 | | | AAT Asn | | | | | | | | 1200 |
| 15 | | | ACT Thr 405 | | | _ | | | | _ | 1248 |
| 20 | | | CCA Pro | | | | | | | | 1296 |
| 20 | | | TGG Trp | | | | | | | | 1344 |
| 25 | | | TCC Ser | | | | | | | | 1392 |
| 30 | | | AAC Asn | | | | | | | | 1440 |
| 35 | | | ATC Ile 485 | | | | | | | | 1488 |
| 40 | | | ATA Ile | | _ | | | | | | 1536 |
| 40 | | | AAG Lys | | | | | | | | 1584 |
| 45 | | | GAT Asp | | | | | | | _ | 1632 |
| 50 | | | GTT Val | | | | | | _ | _ | 1680 |
| 55 | | | AGT Ser 565 | _ | | | _ | | | _ | 1728 |

| | | | | | | | | | | 7 | | | | | | | |
|----|-----|-------|------------|--|----------------------|-----------------------|---------------------|-------------------|----------------|-------------------|-------|-------|-----------|------------|------------|------------------|------|
| _ | | _ | | 5 | 80 | ~ [| SP L | cu P | 5 | ys G 85 | IU L | ys L | eu L | ys G 5 | lu L 90 | TC ATT eu Ile | 1776 |
| 5 | T' | IT G | | AG AG lu Tl 95 | CT G | CT CO | GA T | ie G. | AG Co ln P: | CA G | GA T | AC AC | rg Se | CT TA | AA | | 1818 |
| 10 | | | | (2)] | INFO | TAMS | ON F | OR S | SEQ] | ID No | 0:41: | : | | | | | |
| 15 | | | (E (C | SEQUAL DE SEQUE SE | ENGTH PE: RAND | I: 60 amin EDNE | 5 am o ac SS: | ino id sina | acid | S: Is | | | | | | | |
| 20 | | | (V) | MOL FRAG SEQ | MENT | TYP | E: i | nter | nal | EQ I | D NO | :41: | | | | | |
| 25 | | | l Se | r Ly: | s Gl | y Gl | ı Glı | ı Le | u Ph | e Th | r Gl | y Va | | | | e Leu | |
| | | | | | | | | | | | | | | | | Gly | |
| 30 | Суя | 5 Th: | Thi | c Gly | / Lys | Leu | Pro | Va] | Pro | Tr | Pro | Thr | 45 Let | ı Va] | l Thr | Thr | |
| | | | | | | | | | | | | Pro | | | | Lys 80 Glu | |
| 35 | | | | Phe | Phe | | | | | | | | | | | Glu | |
| | Val | Lys | Phe 115 | Glu | Gly | Asp | Thr | Leu | Val | Asn | Arg | Ile | Glu | 110 Leu | Lys | Gly | |
| 40 | | | | Lys | | | | Asn | Ile | | | | | | | | |
| | | | | Ser | | | | | | | | Asp | | | | | |
| 45 | Val | Gln | Leu | Val Ala 180 | 165 Asp | His | Tyr | Gln | Arg | His 170 Asn | Asn | Ile | Glu | Asp | Gly 175 | Ser | |
| | | | | 180 Leu | | | | His | | | | | | | | | |
| 50 | | | | Pro | | | | | | | | Val | | | | | |
| | | | | Ala | | | Thr | | | | | | | | | | |
| 55 | | | | Ser | | | | | | | Ala | | | | | | |
| - | | | va. | Arg 260 | стА | GIN | val | Phe | Asp 265 | Val | Gly | Pro | Arg | Tyr 270 | Thr | Asn | |

75

```
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
                 280
                                     285
            275
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                          295
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
     305 310
                                        315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                   325
                                    330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
               340
                                 345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
           355
                             360
                                               365
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                          375
                                            380
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
            390
                                        395
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
               . 405
                                    410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
               420
                                425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
           435 440
                                     445
     Gly Tyr Thr´Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                          455
                                            460
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
                    470 475
     Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                                     490
     Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
              500
                                505
                                         510
     Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                             520
                                               525
     Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
       530
                535
                                          540
35
     Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                    550
                                       555
     Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                  565
                                    570 575
     Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
                                585
     Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
                              600
             (2) INFORMATION FOR SEQ ID NO:42:
45
           (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 2529 base pairs
             (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
50
            (D) TOPOLOGY: linear
```

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

55

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2526

76

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

| 5 | 1 | | | | • | 5 | - | | | cu | PIIE | 10 | ir G | ту | Va1 | l Va | 1 P | ro | Ile 15 | C CTG | | 48 |
|----|-------------------|-------------------|--------------------|-----------------|--------------|------------------|-------------------|--------------------|-------------------|----------|------------------|------------------|-------------------|--------------|------------------|-------------------|--------------|------------------------|-----------|-------------------|---|-----|
| 10 | | | | | 20 | 7 | | p vo | · - A | 211 | 25 | , HI | s L | ys | Phe | Se. | r Va 30 | al: | Ser | GGC Gly | | 96 |
| 15 | GA G1: | G G(u G) | GC G ly G | AG lu 5 | GGC Gly | GAT Asp | GC6 | C AC | T Ty | Y L | GGC Gly | Ly: | G C' | ΓG . eu ' | ACC Thr | CTC Let | G AA | AG : | rtc | ATC | | 144 |
| 20 | TG(Cys | C AC S Th | CC A ar T | CC (| GGC Gly | AAG Lys | CTC | G CC 1 Pr 55 | C G1 o Va | rg | CCC Pro | TG(| G CO | 0 (| ACC Thr 60 | CTO | C GI 1 Va | G A | .CC hr | ACC Thr | | 192 |
| | CTC Lev 65 | AC Th | C T | AC C | GC Sly | GTG Val | CAG Gln 70 | TG Cy | C TI S Ph | C . | AGC Ser | CGC | TA Ty 75 | r E | CCC Pro | GAC Asp | CA Hi | C A s M | TG et | AAG Lys 80 | | 240 |
| 25 | CAG Gln | CA Hi | C GA | AC I | | TTC Phe 85 | AAG Lys | TC(Ser | C GC | C A | ATG Met | CCC Pro 90 | GA Gl | A G u G | GC Sly | TAC Tyr | GT(Va. | C C. 1 G. 9: | ln | GAG Glu | | 288 |
| 30 | CGC Arg | AC: | C AT | - | TC the 1 | TTC Phe | AAG Lys | GAC Asp | GA Ası | b c | GC Sly 105 | AAC Asn | TA: | C A | AG ys | ACC Thr | CGC Arg | J A | CC la | GAG Glu | | 336 |
| 35 | GTG Val | AA(| 3 TT 5 Ph 11 | C G e G 5 | AG C | GC Bly | GAC Asp | ACC | CTO Let 120 | 1 V | TG al | AAC Asn | CGG | C A | le (| GAG Glu 125 | CTG Leu | AA Ly | .G 's | GGC Gly | | 384 |
| 40 | ATC Ile | GAC Asp 130 | TT Ph | C AA | AG G /s G | AG (| GAC Asp | GGC Gly 135 | AAC Asn | A I | TC (| CTG Leu | GGC Gly | H | AC A is I | AAG Lys | CTG Leu | GA Gl | Gʻ uʻ | TAC Tyr | | 432 |
| | AAC Asn 145 | TAC Tyr | AA(| C AC | C C | | AAC Asn 150 | GTC Val | TAT Tyr | ' A' | TC A | ATG Met | GCC Ala 155 | As | AC A | -γs | CAG Gln | AA Ly | s A | AAC Asn 160 | | 480 |
| 45 | GGC Gly | ATC Ile | AA0 Lys | G GT Va | | AC I sn F | TC he | AAG Lys | ATC Ile | C(A) | rg H | CAC lis | AAC Asn | AT Il | C G e G | AG lu | GAC Asp | GG(G1 ₂ | 7 S | GC Ser | 5 | 528 |
| 50 | GTG Val | CAG Gln | CTC | GC Al 18 | | AC C | AC 1 | TAC Tyr | CAG Gln | CA Gl | n A | AC . | ACC Thr | CC Pr | C A | le (| GGC Gly | GA(Asp | C G | GC ly | 5 | 76 |
| 55 | CCC (| TG /al | CTG Leu 195 | CT(| G CC | CC G | AC A | 1911 | CAC His 200 | TA Ty | C C | TG / | AGC Ser | ACC Th: | r G | AG 1 ln s | rcc Ser | GCC Ala | C | TG eu | 6 | 24 |

| | | | | | | | 77 | | | | | | | |
|----|------|-------------------|---|---|---|---|-----|---|---|---|---|---|---|------|
| | | CCC Pro | | _ | | | | | | | | _ | | 672 |
| 5 | | GCC Ala | | | | | | | | | | | | 720 |
| 10 | | TCT Ser | | | | | | | | | | | | 768 |
| 15 | | GCC Ala 260 | | | | | | | | | | _ | _ | 816 |
| | | AAA Lys | | | | | | | | | | | | 864 |
| 20 | | AGC Ser | _ | | _ | | | | | | | | | 912 |
| 25 | | TTA Leu | | | | _ | _ | _ | | | | _ | | 960 |
| 30 | | GAA Glu | | | | | | | | | _ | _ | | 1008 |
| 35 | | GCA Ala 340 | | | | | | | | | | | | 1056 |
| 40 | | GAA Glu | _ | | | | | | | | | | | 1104 |
| 40 | | CAA Gln | _ | | _ | | | | _ | | | _ | | 1152 |
| 45 | | AAG Lys | | | | | Phe | | | | | | | 1200 |
| 50 | | TAC Tyr | | | | | | | | | | | | 1248 |
| 55 | | GAC Asp 420 | | | | | | | | _ | | _ | | 1296 |

| | | | | | | | | | | | | 78 | | | | | | | | | |
|----|-------------------|-------------------|--------------------|-----------------------|--------------------|------------------|-------------------|-------------------|-------------------------------|--------------------|------------------|------------|--------------------|--------------------|-------------------|----------------|----------------|-------------------|------------------|-------------------|------|
| | G1 Va | G A | | AAA 1 Lys 1 135 | AAC A | ACT Thr | TTC | AGe Ar | G CA g G] 44 | in T | AT yr | CGA Arg | GT(| G CT l Le | u G | GA Z ly : | AA# | GG G1 | G Y | GGC Gly | 1344 |
| 5 | TT Ph | | GG G ly G 50 | SAG C | TC : | rgr Cys | GCC Ala | Cy: | s GT | .G G' | TT (| CGG Arg | GC0 Ala | C AC a Th 46 | r G. | GT I | AAA Lys | AT Me | G t | TAT Tyr | 1392 |
| 10 | GC A1 46 | 2 | GC A | AG C | GC T | TG eu | GAG Glu 470 | AAC Lys | AA Ly | G AG | ig j | ATC []e | AAA Lys 475 | Ly | G AC | eg A | AAA ys | GG G1 | y (| GAG Glu 480 | 1440 |
| 15 | TC: Se: | C AT | rg g et A | CC C la L | cu n | AT sn 85 | GAG Glu | AAG Lys | GA: | G Al | e I | CTC eu | GAG Glu | AA(| G GT S Va | C A | AC sn | AG' Ser | r (| CAG Gln | 1488 |
| 20 | TT'. Phe | r G1 ≥ Va | G G | TC A | AC C sn L 00 | TG (| GCC Ala | TAT Tyr | GC(| С ТА а Ту 50 | r G | AG lu | ACC Thr | AAC Lys | GA As | p A | CA la 10 | CTC | 3 T | GC Cys | 1536 |
| | TTC Leu | GT Va | C C: 1 Le 5: | rg Ad eu Tl L5 | CC A | TC 1 | ATG Met | AAT Asn | GG(Gl ₃ 520 | / GI | ТG. уА | AC sp | CTG Leu | AAG Lys | TT Ph | е н | AC is | ATC Ile | T | AC Yr | 1584 |
| 25 | AAC Asn | Me 53 | | SC AA | AC Co | CT (| GC Gly | TTC Phe 535 | GAC Glu | GA Gl | G G | AG lu | CGG Arg | GCC Ala 540 | TT | G T | rT ne | TAT Tyr | G A | CG la | 1632 |
| 30 | GCA Ala 545 | | G AT | C CI | C TO | 5 6 | GC Sly 550 | TTA Leu | GAA Glu | GA(| C CT | eu l | CAC His 555 | CGT Arg | GA(| AZ 1 As | AC sn | ACC Thr | V | TC al 60 | 1680 |
| 35 | TAC Tyr | CG/ Arg | A GA J As | T CT p Le | G AA u Ly 56 | 5 P | CT (| GAA Glu | AAC Asn | ATC Ile | C CI Le 57 | eu I | ITA Leu | GAT Asp | GAT Asp | TA Ty | r | GGC Gly 575 | C# | AC is | 1728 |
| 40 | ATT Ile | AGG | AT | C TC e Se 58 | LAS | сс рЬ | TG (| GGC Gly | TTG Leu | GCT Ala 585 | Va | G A | AAG .ys | ATC Ile | CCC Pro | GA G1 59 | u (| GGA Gly | G <i>P</i> As | AC sp | 1776 |
| | CTG Leu | ATC Ile | Arg 595 | C GGG g Gly | C CG Y Ar | G G: g Va | TG (| TA. | ACT Thr 600 | GTT Val | GG G1 | с т у т | AC 'yr i | Met | GCC Ala 605 | CC Pr | C (| GAA Glu | GT Va | C 1 | 1824 |
| 45 | CTG Leu | AAC Asn 610 | AA(Asr | CAC n Glr | AGO Aro | I TA | Y L | GC (ly) | CTG Leu | AGC Ser | CC | C G | sp ' | TAC Tyr 620 | TGG Trp | GG(| C C | CTT Seu | GG G1 | C Y | 1872 |
| 50 | TGC Cys 625 | CTC Leu | ATC | TAT | GAC | TA E Me 63 | : L | TC (| GAG Glu | GGC Gly | CA(Gl | n S | CG (er 1 35 | CCG Pro | TTC Phe | CGG | C G | ly . | CG Ar | g | 1920 |
| 55 | AAG (| GAG Glu | AAG Lys | GTG Val | Lys 645 | MI | ig G | AG G | AG Slu | GTG Val | GAC Asp |) A | GC (| GG (Arg ' | GTC Val | CTC Lev | ı G | AG A | AC(| G r | 1968 |

79

| | | | | | | 79 | | | | |
|------|--|--|-------------------|--|--|----|-----|--|--|------|
| | | | TCC Ser | | | | | | | 2016 |
| 5 | | | ACG Thr | | | | | | | 2064 |
| 10 | | | GAG Glu | | | | | | | 2112 |
| 15 . | | | GAA Glu | | | | | | | 2160 |
| 20 | | | TAC Tyr 725 | | | | | | | 2208 |
| | | | GTC Val | | | | | | | 2256 |
| 25 | | | GGC Gly | | | | | | | 2304 |
| 30 | | | TTT Phe | | | | | | | 2352 |
| 35 | | | CTG Leu | | | | | | | 2400 |
| 40 | | | AGA Arg 805 | | | | | | | 2448 |
| | | | TCC Ser | | | | | | | 2496 |
| 45 | | | AAC. Asn | | | | TAG | | | 2529 |
| | | | | | | | | | | |

50 (2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 842 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single

55

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Ser Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg Glu Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala Cys Ala Gln Ser

| | | | | | | | | | | 01 | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Val | His | Glu | Tyr | Leu 405 | Arg | Gly | Glu | Pro | Phe 410 | His | Glu | Tyr | Leu | Asp 415 | Ser |
| | Met | Phe | Phe | Asp | Arg | Phe | Leu | Gln | Trp 425 | Lys | Trp | Leu | Glu | Arg 430 | Gln | Pro |
| 5 | Val | Thr | Lys 435 | Asn | Thr | Phe | Arg | Gln 440 | Tyr | Arg | Val | Leu | Gly 445 | Lys | Gly | Gly |
| | Phe | Gly 450 | Glu | Val | Cys | Ala | Cys 455 | Gln | Val | Arg | Ala | Thr 460 | Gly | Lys | Met | Tyr |
| 10 | Ala 465 | Суѕ | Lys | Arg | Leu | Glu 470 | Lys | Гуs | Arg | Ile | Lys 475 | Lys | Arg | Lys | Gly | Glu 480 |
| | Ser | Met | Ala | Leu | Asn 485 | Glu | Lys | Gln | Ile | Leu 490 | Glu | Lys | Val | Asn | Ser 495 | Gln |
| | Phe | Val | Val | Asn 500 | Leu | Ala | Tyr | Ala | Tyr 505 | Glu | Thr | Lys | Asp | Ala 510 | Leu | Суз |
| 15 | Leu | Val | Leu 515 | Thr | Ile | Met | Asn | Gly 520 | Gly | Asp | Leu | Lys | Phe 525 | His | Ile | Tyr |
| | Asn | Met 530 | Gly | Asn | Pro | Gly | Phe 535 | Glu | Glu | Glu | Arg | Ala 540 | Leu | Phe | Tyr | Ala |
| 20 | 545 | | Ile | | | 550 | | | - | | 555 | _ | | | | 560 |
| | _ | _ | Asp | | 565 | | | | | 570 | | _ | _ | _ | 575 | |
| | | - | Ile | 580 | _ | | _ | | 585 | | - | | | 590 | _ | |
| 25 | | | Arg 595 | _ | _ | | _ | 600 | | - | - | | 605 | | | |
| | | 610 | Asn | | | | 615 | | | | | 620 | | | | |
| 30 | 625 | | Ile | _ | | 630 | | | _ | | 635 | | | | _ | 640 |
| | _ | | Lys | | 645 | | | | | 650 | _ | | | | 655 | |
| 35 | | | Val Leu | 660 | | | _ | | 665 | | | | _ | 670 | | |
| 33 | - | | 675 Ala | | | _ | _ | 680 | - | | _ | | 685 | - | | |
| | | 690 | Arg | | | | 695 | _ | | | | 700 | _ | | | |
| 40 | 705 | - | Ala | | | 710 | _ | | | _ | 715 | | | | | 720 |
| | | _ | Lys | | 725 | • | • | - | | 730 | - | | | | 735 | |
| 45 | | | - | 740 | | | | - | 745 | | - | - | - | 750 | - | Ile |
| | - | | 755 Glu | | _ | | | 760 | | | - | | 765 | | | |
| | | 770 | Pro | | | | 775 | | | | | 780 | | | | |
| 50 | 785 | | Leu | | | 790 | | | | | 795 | | | | | 800 |
| | • | | Pro | | 805 | | | • | J | 810 | | | | | 815 | - |
| 55 | | | Ser | 820 | | | | | 825 | | | | | 830 | | |
| | | | 835 | | | | | 840 | | | | | | | | |

| | | | | (2) | INFO | RMAT | ION | FOR | SEQ | ID N | 0:44 | : | | | | | |
|----|------------|--------------------|------------|----------------------|-----------------------|-------------------------|---------------------|--------------------|--------------|--------------------|--------------|--------------|-------------|------------|------------|----------------|-----|
| 5 | | | (| A) L B) T C) S | ENGT YPE : TRAN | E CH H: 1 nuc DEDNI | 902 leic ESS: | base aci sin | pai d | S: rs | | | | | | | |
| 10 | | | (ii (ix |) MO | LECU ATUR | LE T | YPE: | cDN | A. | | | | | | | | |
| 15 | | | | (B) | LOCA! | /KEY: TION: R INF | 1. | 189 | 9 | ience | : | | | | | | |
| | | | (xi) | SEC | QUENC | CE DE | SCR | PTIC | N: S | EQ I | D NO | :44: | | | | | |
| 20 | 1 | | rg Ac | GC AF | AG GO 's Gl | GC GA y Gl | .G GA u Gl | AG CT .u Le | G TT u Ph | C AC e Th 10 | C GG r Gl | G GT y Va | G GT | l Pr | 0 Il 15 | C CTG e Leu | 48 |
| 25 | | | | 20 | P 01 | y ns | p va | I AS | n G1; | у ні: | s Ly: | s Ph | e Se: | 7 Va 30 | l Se | C GGC r Gly | 96 |
| 30 | | | 35 | | , | p Ale | 4 111. | 40 | r GI | / Lys | . Lei | 1 Th: | r Lei 45 | ı Lys | s Phe | C ATC | 144 |
| | TG(| C AC S Th 50 | C AC | C GGG | C AAG Y Lys | G CTC | CCC Pro | C GTO Val | G CCC | TGG Trp | CCC Pro | ACC Thi | CTC Leu | GTC Val | ACC Thr | ACC Thr | 192 |
| 35 | 65 | | • | 1 | | G CAG I Gln 70 | . Cys | PHE | ser | Arg | 75 | Pro | Asp | His | Met | Lys 80 | 240 |
| 40 | | | • | | 85 | AAG Lys | Ser | мта | мес | 90 | Glu | Gly | Tyr | Val | Gln 95 | Glu | 288 |
| 45 | | | | 100 | | AAG Lys | АБР | Asp | 105 | Asn | Tyr | Lys | Thr | Arg 110 | Ala | Glu | 336 |
| 50 | | • | 115 | | Cry | GAC Asp | 1111 | 120 | vai | Asn | Arg | Ile | Glu 125 | Leu | Lys | Gly | 384 |
| | | 130 | | -, - | 014 | GAC Asp | 135 | ASII | TIE | Leu | Gly | His 140 | Lys | Leu | Glu | Tyr | 432 |
| 55 | AAC Asn | TAC Tyr | AAC Asn | AGC Ser | CAC His | AAC Asn | GTC Val | TAT Tyr | ATC Ile | ATG Met | GCC Ala | GAC Asp | AAG Lys | CAG Gln | AAG Lys | AAC Asn | 480 |

| | 145 | | | 150 | | | 155 | | | | 160 | |
|----|-----|------|-------------------|-----|--|--|-----|--|---|---|-----|------|
| 5 | | | AAC Asn 165 | | | | | | | | | 528 |
| 10 | | | GAC Asp | | | | | | | | _ | 576 |
| | | | CCC Pro | | | | | | | _ | | 624 |
| 15 | | | AAC Asn | | | | | | | | | 672 |
| 20 | | | GGG Gly | | | | | | | | | 720 |
| 25 | | | CGA Arg 245 | | | | | | | | | 768 |
| 30 | | | AGT Ser | | | | | | | | | 816 |
| | | | AAT Asn | | | | | | | | | 864 |
| 35 | | | TAT Tyr | | | | | | _ | | | 912 |
| 40 | | | CCA Pro | | | | | | | | | 960 |
| 45 | | | CTT Leu 325 | | | | | | | | | 1008 |
| 50 | | | TTC Phe | | | | | | | _ | | 1056 |
| 50 | | | ATG Met | | | | | | | | | 1104 |
| 55 | | | GAT Asp | | | | | | | _ | | 1152 |

| | 370 | | 375 | ` | 380 | | |
|----|-------------------------------|--|------------------------------------|---------------------------------|-------------------------------------|---|------|
| E | CTG TGT Leu Cys | GGA ATC A | AG CAC CTT ys His Leu | CAT TCT (| | ATT CAT CGG GAC Ile His Arg Asp | 1200 |
| 5 | TTA AAG | CCC AGT A | AT ATA GTA | ርጥል አአአ ጥ | 395 | 400 | 10.0 |
| 10 | • | 4(|)5 | vai Lys S | er Asp Cys ' 110 | Thr Leu Lys Ile 415 | 1248 |
| | • | 420 | A AIG AIG | 425 | ily Thr Ser I | TTT ATG ATG ACG Phe Met Met Thr 430 | 1296 |
| 15 | • | GTA GTG AC Val Val Th 435 | r Arg Tyr | TAC AGA G Tyr Arg A 440 | la Pro Glu V | GTC ATC CTT GGC Val Ile Leu Gly | 1344 |
| 20 | ATG GGC Met Gly 450 | TAC AAG GA Tyr Lys Gl | A AAC GTG ou u Asn Val ; 455 | GAT TTA TO Asp Leu Ti | GG TCT GTG G rp Ser Val G 460 | GGG TGC ATT ATG | 1392 |
| 25 | 465 | ······································ | 470 | rie ren b | ne Pro Gly A 475 | GG GAC TAT ATT rg Asp Tyr Ile 480 | 1440 |
| 30 | GAT CAG T Asp Gln T | IGG AAT AA! Irp Asn Lys 485 | , var ite (| GAA CAG CT Glu Gln Le 49 | eu Gly Thr P | CA TGT CCT GAA ro Cys Pro Glu 495 | 1488 |
| | TTC ATG A | AAG AAA CTO Lys Lys Leu 500 | CAA CCA A Gln Pro T | ACA GTA AG Thr Val Ar 505 | G ACT TAC G | IT GAA AAC AGA al Glu Asn Arg 510 | 1536 |
| 35 | CCT AAA T Pro Lys T | AT GCT GGA Yr Ala Gly 15 | TAT DEL D | TT GAG AA he Glu Ly: 20 | A CTC TTC CC s Leu Phe Pr 52 | CT GAT GTC CTT TO Asp Val Leu | 1584 |
| 40 | TTC CCA G Phe Pro A 530 | CT GAC TCA la Asp Ser | GAA CAC A Glu His A 535 | AC AAA CT sn Lys Let | T AAA GCC AG u Lys Ala Se 540 | ET CAG GCA AGG er Gln Ala Arg | 1632 |
| | 545 | | 550 | ai iie Asp | P Ala Ser Ly 555 | A AGG ATC TCT s Arg Ile Ser 560 | 1680 |
| 50 | GTA GAT GA Val Asp Gl | AA GCT CTC lu Ala Leu 565 | CAA CAC CC Gln His Pr | CG TAC ATO ro Tyr Ile 570 | e Asn Val Tr | G TAT GAT CCT p Tyr Asp Pro 575 | 1728 |
| | TCT GAA GC Ser Glu Al | CA GAA GCT la Glu Ala 580 | CCA CCA CC Pro Pro Pr | CA AAG ATC CO Lys Ile 585 | CCT GAC AAG | G CAG TTA GAT s Gln Leu Asp 590 | 1776 |
| 55 | GAA AGG GA Glu Arg Gl | A CAC ACA u His Thr | ATA GAA GA Ile Glu Gl | G TGG AAA u Trp Lys | GAA TTG ATA Glu Leu Ile | A TAT AAG GAA E Tyr Lys Glu | 1824 |

85

600 595 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872 Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 615 620 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 630 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 85 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 190 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 195 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 230 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

250

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Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
                   260
                        265
        Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
                          280
        Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
   5
                             295
       Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
                         310
                                              315
       Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
  10
                      325
                                         330
       Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
                 340
                                     345
       Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
                                  360
       Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
  15
                             375
                                                380
       Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
                         390
                                            395
       Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
 20
                      405
                                         410
       Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
                  420
                                     425
       Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
                                                        430
                                 440
 25
       Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
                                                   445
                             455
      Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
                                      460
                         470
                                            475
      Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
 30
                                        490
      Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
                  500
                                   505
      Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
                                520
      Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
                                            525
35
                   535
      Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
                        550
                                            555
      Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
40
                     565
                                        570
      Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
                                    585
     Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
                                600
     Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
45
                           615
     Pro Ser Pro Leu Ala Gln Val Gln Gln
50
              (2) INFORMATION FOR SEQ ID NO:46:
```

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1824 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

87

(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1821

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

| | | () | ci) S | SEQUE | ENCE | DESC | CRIP | CION | SEÇ |) ID | NO:4 | 16: | | | | | |
|----|----------|------|----------|----------------------|----------|------|------|------|-----|------|-------|-------|------|-----|------|-----|-----|
| 10 | | | | | | | | | | | | | | | | | |
| | | | | AAG | | | | | | | | | | | | | 48 |
| | Met 1 | vaı | ser | Lys | GIY 5 | GIU | GIU | Leu | Pne | | GIÀ | vaı | vaı | Pro | 11e | Leu | |
| | 1 | | | | 5 | | | | | 10 | | | | | 13 | | |
| 15 | GTC | GAG | CTG | GAC | GGC | GAC | GTA | AAC | GGC | CAC | AAG | TTC | AGC | GTG | TCC | GGC | 96 |
| | | | | Asp | | | | | | | | | | | | | |
| | | | | 20 | • | • | | | 25 | | - | | | 30 | | - | |
| | | | | | | | | | | | | | | | | | |
| | GAG | GGC | GAG | GGC | GAT | GCC | ACC | TAC | GGC | AAG | CTG | ACC | CTG | AAG | TTC | ATC | 144 |
| 20 | Glu | Gly | Glu | Gly | Asp | Ala | Thr | Tyr | Gly | Lys | Leu | Thr | Leu | Lys | Phe | Ile | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | GGC | | | | | | | | | | | | | 192 |
| 25 | Cys | 50 | The | Gly | гус | Leu | 55 | vaı | Pro | Trp | Pro | 60 | Leu | vai | Thr | THE | |
| LJ | | 50 | | | | | 33 | | | | | 80 | | | | | |
| | CTG | ACC | TAC | GGC | GTG | CAG | TGC | TTC | AGC | CGC | TAC | CCC | GAC | CAC | ATG | AAG | 240 |
| | | | | Gly | | | | | | | | | | | | | |
| | 65 | | - | _ | | 70 | - | | | _ | 75 | | - | | | 80 | |
| 30 | | | | | | | | | | | | | | | | | |
| | CAG | CAC | GAC | TTC | TTC | AAG | TCC | GCC | ATG | CCC | GAA | GGC | TAC | GTC | CAG | GAG | 288 |
| | Gln | His | Asp | Phe | | Lys | Ser | Ala | Met | | Glu | Gly | Tyr | Val | | Glu | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| 35 | ccc | 200 | 3.000 | mmc | mma | *** | CZC | an a | aaa | 777 | m 2 C | 7 7 C | 7.00 | 000 | aaa | CAC | 336 |
| 33 | | | | TTC Phe | | | | | | | | | | | | | 330 |
| | AL 9 | 1111 | 110 | 100 | FIIC | БуS | тэр | nsp | 105 | MSII | TYL | Буз | 1111 | 110 | AIG | GIU | |
| | | | | | | | | | 100 | | | | | | | | |
| | GTG | AAG | TTC | GAG | GGC | GAC | ACC | CTG | GTG | AAC | CGC | ATC | GAG | CTG | AAG | GGC | 384 |
| 40 | Val | Lys | Phe | Glu | Gly | Asp | Thr | Leu | Val | Asn | Arg | Ile | Glu | Leu | Lys | Gly | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | AAG | | | | | | | | | | | | | 432 |
| 45 | 11e | | Phe | Lys | GIu | Asp | | Asn | He | Leu | GIY | | Lys | Leu | Glu | Tyr | |
| 40 | | 130 | | | | | 135 | | | | | 140 | | | | | |
| | AAC | TAC | AAC | AGC | CAC | AAC | GTC | тат | ATC | ATG | GCC | GAC | AAG | CAG | AAG | AAC | 480 |
| | | | | Ser | | | | | | | | | | | | | 100 |
| | 145 | . 4 | - | | | 150 | | -1- | | | 155 | 2 | -1-2 | | -1-2 | 160 | |
| 50 | | | | | | | | | | | | | | | | | |
| | GGC | ATC | AAG | GTG | AAC | TTC | AAG | ATC | CGC | CAC | AAC | ATC | GAG | GAC | GGC | AGC | 528 |
| | Gly | Ile | Lys | Val | Asn | Phe | Lys | Ile | Arg | His | Asn | Ile | Glu | Asp | Gly | Ser | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| cc | a=* | | - | | | a | | | | | | | | | | | |
| 55 | | | | GCC | | | | | | | | | | | | | 576 |
| | val | GIU | Leu | Ala | Asp | HIS | ıyr | GIN | GIN | Asn | Thr | Pro | тте | GIĀ | Asp | GIÀ | |

| | | | | 00 | |
|----|-----------------------------------|--|---|--|-----------------------------|
| | | 180 | 185 | 190 | |
| 5 | CCC GTG C Pro Val L 1 | TG CTG CCC GA eu Leu Pro As 95 | AC AAC CAC TAC sp Asn His Tyr 200 | CTG AGC ACC CAG TCC G Leu Ser Thr Gln Ser A 205 | GCC CTG 624 Ala Leu |
| 10 | AGC AAA G Ser Lys A 210 | AC CCC AAC GA sp Pro Asn Gl | AG AAG CGC GAT lu Lys Arg Asp 215 | CAC ATG GTC CTG CTG G His Met Val Leu Leu G 220 | AG TTC 672 |
| | GTG ACC GG Val Thr A 225 | CC GCC GGG AT la Ala Gly Il 23 | e int red GIA | ATG GAC GAG CTG TAC A Met Asp Glu Leu Tyr L 235 | AG TCC 720 ys Ser 240 |
| 15 | • | 245 | y bys Met Ser (| CAG GAG AGG CCC ACG T Gln Glu Arg Pro Thr Ph 250 | ne Tyr 55 |
| 20 | CGG CAG GA Arg Gln Gl | AG CTG AAC AAC u Leu Asn Lys 260 | G ACA ATC TGG (s Thr Ile Trp (265 | GAG GTG CCC GAG CGT TA Glu Val Pro Glu Arg Ty 270 | AC CAG 816 vr Gln |
| 25 | AAC CTG TC Asn Leu Se 27 | · · · · · · · · · | C TCT GGC GCC T y Ser Gly Ala T 280 | TAT GGC TCT GTG TGT GC Tyr Gly Ser Val Cys Al 285 | T GCT 864 a Ala |
| 30 | TTT GAC AC. Phe Asp Th: 290 | A AAA ACG GGG r Lys Thr Gly | G TTA CGT GTG G Leu Arg Val A 295 | CA GTG AAG AAG CTC TC la Val Lys Lys Leu Se 300 | C AGA 912 r Arg |
| | CCA TTT CAC Pro Phe Glr 305 | G TCC ATC ATT n Ser Ile Ile 310 | Ara bys A | GA ACC TAC AGA GAA CTO rg Thr Tyr Arg Glu Leo 315 | G CGG 960 u Arg 320 |
| 35 | TTA CTT AAF Leu Leu Lys | A CAT ATG AAA 3 His Met Lys 325 | nis Giu Asn Va | TG ATT GGT CTG TTG GAG al lle Gly Leu Leu Asp 30 335 | Val |
| 40 | TTT ACA CCT Phe Thr Pro | GCA AGG TCT Ala Arg Ser 340 | CTG GAG GAA TT Leu Glu Glu Ph 345 | FC AAT GAT GTG TAT CTG ne Asn Asp Val Tyr Leu 350 | G GTG 1056 I Val |
| 45 | ACC CAT CTC Thr His Leu 355 | ATG GGG GCA Met Gly Ala | GAT CTG AAC AA Asp Leu Asn As 360 | AC ATT GTG AAA TGT CAG En Ile Val Lys Cys Gln 365 | AAG 1104 Lys |
| 50 | CTT ACA GAT Leu Thr Asp 370 | mp mis vai | CAG TTC CTT AT Gln Phe Leu Il 375 | C TAC CAA ATT CTC CGA e Tyr Gln Ile Leu Arg 380 | GGT 1152 Gly |
| | CTA AAG TAT Leu Lys Tyr 385 | ATA CAT TCA Ile His Ser 390 | GCT GAC ATA AT Ala Asp Ile Il | T CAC AGG GAC CTA AAA e His Arg Asp Leu Lys 395 | CCT 1200 Pro 400 |
| 55 | AGT AAT CTA Ser Asn Leu | GCT GTG AAT (Ala Val Asn (| GAA GAC TGT GAG Glu Asp Cys Glu | G CTG AAG ATT CTG GAT Leu Lys Ile Leu Asp | TTT 1248 Phe |

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89

| | | | 405 | | | 410 | | | 415 | | |
|----|-------------------|--|-----|--|---|-----|---|--|-----|-----|------|
| 5 | CTG Leu | | | | | | | | | | 1296 |
| 10 | TGG Trp | | | | | | | | | | 1344 |
| | ACA Thr 450 | | | | | | | | | | 1392 |
| 15 | GGA Gly | | | | | | | | | | 1440 |
| 20 | ATT Ile | | | | | | | | | | 1488 |
| 25 | TCC Ser | | | | | | | | | | 1536 |
| 20 | AAG Lys | | | | | | | | | | 1584 |
| 30 | GAC Asp 530 | | | | | | | | | | 1632 |
| 35 | GCG Ala | | | | | | | | | | 1680 |
| 40 | GAT Asp | | | | | | | | | | 1728 |
| 45 | GAC Asp | | | | _ | _ | - | | | | 1776 |
| 50 | AGC Ser | | | | | | | | | TGA | 1824 |
| 50 | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 607 amino acids
 (B) TYPE: amino acid

90

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(C) STRANDEDNESS: single
```

(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 15 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 75 20 85 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 25 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 140 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 30 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 35 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 Gly Leu Arg Ser Arg Gly Lys Met Ser Gln Glu Arg Pro Thr Phe Tyr 40 245 250 Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln 265 Asn Leu Ser Pro Val Gly Ser Gly Ala Tyr Gly Ser Val Cys Ala Ala 280 Phe Asp Thr Lys Thr Gly Leu Arg Val Ala Val Lys Lys Leu Ser Arg 45 295 Pro Phe Gln Ser Ile Ile His Ala Lys Arg Thr Tyr Arg Glu Leu Arg 310 315 Leu Leu Lys His Met Lys His Glu Asn Val Ile Gly Leu Leu Asp Val 50 330 Phe Thr Pro Ala Arg Ser Leu Glu Glu Phe Asn Asp Val Tyr Leu Val 345 Thr His Leu Met Gly Ala Asp Leu Asn Asn Ile Val Lys Cys Gln Lys 360 Leu Thr Asp Asp His Val Gln Phe Leu Ile Tyr Gln Ile Leu Arg Gly 55 375

| | | | | | | | | | | 91 | | | | | | | |
|----|-----|------------|------------|------------|------------|----------|------------|------------|------------|------------|------|------------|------------|------------|------------|-----|-----|
| | | Lys | Tyr | Ile | His | Ser | Ala | Asp | Ile | Ile | His | Arg | Asp | Leu | Lys | Pro | |
| | 385 | | _ | | | 390 | ~3 | | _ | ~ 7 | 395 | | | _ | _ | 400 | |
| | ser | Asn | Leu | Ala | Val 405 | Asn · | GIU | Asp | Cys | 410 | Leu | Lys | 11e | Leu | 415 | Pne | |
| 5 | Gly | Leu | Ala | Arg | His | Thr | Asp | Asp | Glu 425 | | Thr | Gly | Tyr | Val | | Thr | |
| | Arg | Trp | Tyr 435 | | Ala | Pro | Glu | Ile 440 | | Leu | Asn | Trp | Met | | Tyr | Asn | |
| | Gln | Thr | | Asp | Ile | Trp | Ser | | Gly | Cys | Ile | Met | | Glu | Leu | Leu | |
| 10 | | 450 | | • | | - | 455 | | • | | | 460 | | | | | |
| | | Gly | Arg | Thr | Leu | | Pro | Gly | Thr | qaA | | Ile | Asp | Gln | Leu | - | |
| | 465 | T10 | T.e.u | λrα | Leu | 470 | Clv | Thr | Dro | Glv | 475 | Glu | T.A.I | T.All | Lve | 480 | |
| | ьеи | 116 | Leu | Arg | 485 | val | GIY | 1111 | PIO | 490 | мта | GIU | neu | neu | 495 | цуб | |
| 15 | Ile | Ser | Ser | Glu 500 | Ser | Ala | Arg | Asn | Tyr 505 | Ile | Gln | ser | Leu | Thr 510 | Gln | Met | |
| | Pro | Lys | Met 515 | Asn | Phe | Ala | Asn | Val 520 | Phe | Ile | Gly | Ala | Asn 525 | Pro | Leu | Ala | |
| 20 | Val | Asp 530 | Leu | Leu | Glu | Lys | Met 535 | Leu | Val | Leu | Asp | Ser 540 | qaA | Lys | Arg | Ile | |
| 20 | Thr | | Ala | Gln | Ala | Leu | | His | Ala | Tyr | Phe | | Gln | Tyr | His | Asp | |
| | 545 | | | | | 550 | | | | - | 555 | | | - | | 560 | |
| | Pro | Asp | Asp | Glu | Pro 565 | Val | Ala | Asp | Pro | Tyr 570 | Asp | Gln | Ser | Phe | Glu 575 | Ser | |
| 25 | Arg | Asp | Leu | Leu 580 | Ile | Asp | Glu | Trp | Lys 585 | Ser | Leu | Thr | Tyr | Asp 590 | Glu | Val | |
| | Ile | Ser | Phe | _ | Pro | Pro | Pro | Leu | | Gln | Glu | Glu | Met | | Ser | | |
| | | | 595 | | | | | 600 | | | | | 605 | | | | |
| 30 | | | (2) | INI | FORM | OITA | FOI | R SE | Q ID | NO:4 | 18: | | | | | | |
| | | 7.4 | () et | ויפודורים | NCE (| יסמטי | OTE | o T C TT | rce. | | | | | | | | |
| | | \ - | | | STH: | | | • | | | | | | | | | |
| | | | | | E: nu | | | | | | | | | | | | |
| 35 | | | | | ANDEI | | | _ | 2 | | | | | | | | |
| | | | (D) | TOPO | OLOGY | (: 11 | neai | r | | | | | | | | | |
| | | (i | ii) N | OLE | CULE | TYPE | E: cI | ANC | | | | | | | | | |
| 40 | | i) | ix) I | FEAT | JRE: | | | | | | | | | | | | |
| 40 | | | (A) | NAN | ME/KE | EY: (| odir | na Se | emier | ice | | | | | | | |
| | | | | | CATIO | | | | - 4 | | | | | | | | |
| | | | (D) | OTI | HER] | NFO | TAM | ON: | | | | | | | | | |
| 45 | | () | (i) S | EQUE | ENCE | DESC | RIP | CION | : SEC | O ID | NO:4 | 18: | | | | | |
| | | | | _ | | | | | | _ | | | | | | | |
| | | | | | GGC Gly | | | | | | | | | | | | 48 |
| | 1 | vai | Ser | пуз | 5 | Giu | Giu | neu | FIIC | 10 | GIY | vai | vaı | FIO | 15 | пси | |
| 50 | | | | | | | | | | | | | | | | | |
| | | | | | GGC | | | | | | | | | | | | 96 |
| | Val | Glu | Leu | Asp 20 | Gly | Asp | Val | Asn | Gly 25 | His | Lys | Phe | Ser | Val 30 | ser | GIÀ | |
| | | | | ~ 0 | | | | | 23 | | | | | J J | | | |
| 55 | | | | | GAT | - | | | | | | | | | | | 144 |
| | Glu | Gly | Glu | Gly | Asp | Ala | Thr | Tyr | Gly | Lys | Leu | Thr | Leu | Lys | Phe | Ile | |
| | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | 92 | ? | | | | | | | | |
|----|----------------|------------|----------------|------------|--------------|------------|-------------------|--------------------|---------------|------------|--------------|------------|------------|----------------|-------------------|------------|--------------|------------|----------|------------------|-----|
| | | | | 35 | | | | | | 40 | | | | | | 45 | | | | | |
| 5 | C) | | ACC Thr | AC Th | C GO | SC A. | AG C | eu P | CC ro 5 | GT(| G CC L Pr | C T(| G C | ro | ACC Thr 60 | CTC | C GT u Va | G A | CC hr | ACC Thr | 192 |
| 10 | CT Le 65 | G A | ACC | TA Ty | C GG | C G | rg c al g 7 | 111 C | GC ys | TTC Phe | E AG | C CG | g T | AC 'yr 5 | CCC | GA(| C CA | CA' SM | rg et | AAG Lys 80 | 240 |
| | | | | , | | 85 | ie D | AG T | er. | АТА | . Mei | 90 | o G | lu | Gly | Туг | Va. | 1 G] 95 | ln i | Glu | 288 |
| 15 | | - | | | 10 | 0 | .e n | AG GA | sp A | ASP | 105 | / As: | n T | yr | Lys | Thr | 110 |) 3 YJ | .a | Glu | 336 |
| 20 | | _ | , - | 115 | | . 01 | у Ас | C AC | 11. 1 | Leu 120 | vaı | Ası | n Aı | rg | Ile | Glu 125 | Let | ı Ly | s | Gly | 384 |
| 25 | AT(| | AC sp 30 | TTC Phe | Ly: | G GA | G GA u As | C GC p G1 13 | УР | AAC Asn | ATC | Let | G GC | Ly : | CAC His 140 | AAG Lys | CTG | GA Gl | G u | TAC Tyr | 432 |
| 30 | 145 | 5 | | | 501 | | 15 | | 1 1 | yr | 11e | Met | 15 | .a 2 | Asp | ГЛЗ | Gln | Ly | s ; | Asn 160 | 480 |
| | | | | -,- | , u 1 | 165 | i | C AA | s T | те | Arg | His 170 | As | n] | lle | Glu | Asp | Gly 175 | 7 5 | Ser | 528 |
| 35 | | | | | 180 | voř | , ur: | TAC Ty | r G. | ın | GIn 185 | Asn | Th | r F | ro | Ile | Gly 190 | Asp | • • | Sly | 576 |
| 40 | | | 1 | .95 | Deu | 110 | ASI | AA(Asr | 20 | 00 | Tyr | Leu | Sei | r T | hr (| 31n 205 | Ser | Ala | L | eu | 624 |
| 45 | | 21 | 0 | | | ASII | GIU | AAC Lys 215 | AI | eg A | Asp | His | Met | 2 V | al I 20 | leu : | Leu | Glu | P | he | 672 |
| 50 | 225 | | | | ···· | Gly | 230 | | ьe | eu (| зтÀ | Met | Asp 235 | G. | lu I | eu 1 | Гуr | Lys | 2 | er 40 | 720 |
| | GGA Gly | | | -5 | | 245 | per | AIA | GI | uc | ily | Tyr 250 | Gln | T | yr A | rg A | Ala | Leu 255 | Ty | yr | 768 |
| 55 | GAT Asp | TAT Tyr | L | AA I | AAG Lys | GAA Glu | AGA Arg | GAA Glu | GA Gl | A G u A | AT : | ATT Ile | GAC Asp | TT Le | rg c eu H | AC 1 | TTG eu | GGT Gly | GA As | AC sp | 816 |

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| | | | | | | | | | | 93 | | | | | | | |
|-----|------|------|------|-----|------|-----|-----|-----|------|-------------------|-----|-----|-----|-----|-----|-----|------|
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | מידמ | TTC | aст | стс | ידממ | מממ | GGG | TCC | ттΔ | GTA | GCT | СТТ | GGA | ттс | ΔСТ | GAT | 864 |
| 5 | | | | | | | | | | Val | | | | | | | 004 |
| | | _ | | | | | | | | GGC Gly | | | | | | | 912 |
| 10' | | ACC | | | | | GGG | | | CCG | | ACT | | _ | _ | | 960 |
| | 305 | 1111 | 1111 | GIY | Giu | 310 | Gly | Asp | FIIC | Pro | 315 | | IYL | Val | Giu | 320 | |
| 15 | | | | | | | | | | ACA Thr 330 | | | | | | | 1008 |
| 20 | | | | | | | | | | TCG Ser | | | | | | | 1056 |
| | | | | GCT | | | | | GAT | CTT Leu | | | | TTT | | | 1104 |
| 25 | O.L. | 0111 | 355 | | 200 | | 200 | 360 | | ,200 | | 022 | 365 | | | | |
| 20 | | | | | | | | | | AAG Lys | | | | | | | 1152 |
| 30 | | | | | | | | | | TAC Tyr | | | _ | | | | 1200 |
| 35 | | | | | | | _ | | | GAT Asp 410 | | | | | | _ | 1248 |
| 40 | | | | | | | | | | TTG Leu | | | | | | | 1296 |
| 45 | | | | | | _ | | | | ATT Ile | | | | | - | | 1344 |
| 50 | | | | | | | | | | CAA Gln | | | | | | | 1392 |
| 50 | | | | | | | | | | CCT Pro | | | | | | | 1440 |
| 55 | | | | | | | | | | CAT His | | | | | | | 1488 |

| | | | | | | | | | | | 94 | | | | | | | | |
|----|-------------------------|---------------------|------------------------------|--------------------|-------------------|-------------------|--------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|--------------------|-------------------|----------|-------------------|------|
| | | | | | 48 | | | | | | 490 | | | | | | 95 | | |
| 5 | ACC Thr | TCC Ser | AGC Ser | AAA Lys 500 | | CT Le | G TI u Le | rg Az eu As | in P | SCA Ala 505 | AGA Arg | A GT. | A CT l Le | C TC' u Se: | T GA r Gl 51 | u I | гт le | TTC Phe | 1536 |
| 10 | AGC Ser | CCT Pro | ATG Met 515 | CTT Leu | TTC | AG Arg | A TI | C TO e Se 52 | : A | CA la | GCC Ala | Sei | C TC | r GA: r Ası 525 | As | T AC | CT 1r | GAA Glu | 1584 |
| | AAC Asn | CTC Leu 530 | ATA Ile | AAA Lys | GTT Val | ATA Ile | A GA = G1 53 | u 11 | T T e L | TA eu | ATC Ile | TCA Ser | A ACT | Glu | A TG | G AA P As | n | GAA Glu | 1632 |
| 15 | CGA (Arg (545 | CAG Gln | CCT Pro | GCA Ala | CCA Pro | GCA Ala 550 | пе | G CC u Pr | T C | CT ro | AAA Lys | CCA Pro | Pro | AAA Lys | CC: | r AC | r | ACT Thr 560 | 1680 |
| 20 | GTA (| GCC . Ala . | AAC Asn | AAC Asn | GGT Gly 565 | ATG Met | AA: Ası | r AA n Ası | C AZ | sn | ATG Met 570 | TCC Ser | TTA Leu | CAA Gln | AA] Asr | GC Al. | a (| GAA Glu | 1728 |
| 25 | TGG T | TAC : | | GGA Gly 580 | GAT Asp | ATC Ile | TCC | AGO Arg | G G# G G1 58 | .u (| GAA Glu | GTG Val | AAT Asn | GAA Glu | AAA Lys 590 | Le | T (| CGA Arg | 1776 |
| 30 | GAT A Asp T | | GCA (Ala <i>A</i> 595 | GAC Asp | GGG Gly | ACC Thr | TTT Phe | Leu 600 | t va | 'A (| CGA Arg | GAT Asp | GCG Ala | TCT Ser 605 | ACT Thr | AA/ Lys | A A | ATG Met | 1824 |
| | CAT G His G | GT G ly A 10 | AT 1 | TAT I | ACT Thr | CTT Leu | ACA Thr 615 | CTA Leu | AG Ar | G A | ys AAA | GGG Gly | GGA Gly 620 | AAT Asn | AAC Asn | AAA Lys | L | TA eu | 1872 |
| 35 | ATC AM Ile Ly 625 | AA A ys I | TA T le P | TT (| 113 | CGA Arg 630 | GAT Asp | GGG Gly | AA. Ly: | A I | yr (| GGC Gly 635 | TTC Phe | TCT Ser | GAC Asp | CCA Pro | L | TA eu 40 | 1920 |
| 40 | ACC TT | rc A | GT T er S | | TG (al v | GTT /al | GAA Glu | TTA Leu | ATZ Ile | • A | AC (sn 1 | CAC His | TAC Tyr | CGG Arg | AAT Asn | GAA Glu 655 | To Se | CT er | 1968 |
| 45 | CTA GC Leu Al | ET CA | | AT A yr A 60 | AT (| ccc . Pro : | AAA Lys | TTG Leu | GAT Asp | V. | TG A | AAA | TTA Leu | Leu ' | TAT Tyr 670 | CCA Pro | GT Va | ra al | 2016 |
| 50 | TCC AA Ser Ly | A TA 'S Ty 67 | | AA C | AG G ln A | AT (| 3111 | GTT Val 680 | GTC Val | L) | AA G /s G | AA (| Asp A | AAT A Asn 1 | ATT Ile | GAA Glu | GC Al | CT la | 2064 |
| • | GTA GG Val Gl | G AA y Ly 0 | A AA | AA T | TA C | 15 (| GAA Glu G95 | TAT Tyr | AAC Asn | AC Th | et c | ln E | TTT (Phe (| CAA (Gln (| SAA Slu | AAA Lys | AG Se | T :r | 2112 |
| 55 | CGA GAZ Arg Gli | А ТА и Ту | T GA r As | T AC | SA T | TA 1 eu 1 | AT (| GAA Glu | GAA Glu | ТА | T A | CC C | GC A | CA Thr S | CCC (Ser (| CAG Gln | GA Gl | A u | 2160 |

| | 705 | | | 710 | | | | 715 | | | | 720 | |
|----|-----|-----------------------|--|-----|---|---|--|-----|--|---|---|-----|------|
| 5 | | ATG Met | | | | | | | | | | | 2208 |
| 10 | | GAA Glu | | | | | | | | | | | 2256 |
| | | AAG Lys 755 | | | | | | | | _ | | _ | 2304 |
| 15 | | AAT Asn | | | | | | | | | | | 2352 |
| 20 | | AGA Arg | | | | | | | | _ | _ | | 2400 |
| 25 | | ATT Ile | | | | | | | | | | | 2448 |
| 30 | | AAG Lys | | | | | | | | _ | | | 2496 |
| 00 | | CAA Gln 835 | | | | _ | | | | | _ | | 2544 |
| 35 | | TAT Tyr | | _ | _ | | | | | _ | | | 2592 |
| 40 | | ACA Thr | | | | | | | | | | | 2640 |
| 45 | | CGA Arg | | | | | | | | | | | 2688 |
| 50 | | GGC Gly | | | | | | | | | | | 2736 |
| Ju | | GTC Val 915 | | | | | | | | | | | 2784 |
| 55 | | TTG Leu | | | | | | | | | | | 2832 |

96

930 935 ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr 2880 5 950 955 CCA GTA TAT GCA CAG CAG AGG CGA TGA Pro Val Tyr Ala Gln Gln Arg Arg 2907 965

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15

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(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 968 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:
- 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 140 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 45 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 190 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 195 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser

230

Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr

250

| | | | | | | | | | | 91 | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Asp | Tyr | Lys | Lys 260 | Glu | Arg | Glu | Glu | Asp 265 | Ile | Asp | Leu | His | Leu 270 | Gly | Asp |
| | Ile | Leu | Thr 275 | Val | Asn | Lys | Gly | Ser 280 | Leu | Val | Ala | Leu | Gly 285 | Phe | Ser | Asp |
| 5 | Gly | Gln 290 | Glu | Ala | Arg | Pro | Glu 295 | Glu | Ile | Gly | Trp | Leu 300 | Asn | Gly | Tyr | Asn |
| | Glu 305 | Thr | Thr | Gly | Glu | Arg 310 | Gly | Asp | Phe | Pro | Gly 315 | Thr | Tyr | Val | Glu | Tyr 320 |
| 10 | Ile | Gly | Arg | Lys | Lys 325 | Ile | Ser | Pro | Pro | Thr 330 | Pro | Lys | Pro | Arg | Pro 335 | Pro |
| | Arg | Pro | Leu | Pro 340 | Val | Ala | Pro | Gly | Ser 345 | Ser | Lys | Thr | Glu | Ala 350 | Asp | Val |
| | Glu | Gln | Gln 355 | Ala | Leu | Thr | Leu | Pro 360 | Asp | Leu | Ala | Glu | Gln 365 | Phe | Ala | Pro |
| 15 | | 370 | Ile | | | | 375 | | | • | | 380 | | | | |
| | 385 | _ | Gly | | | 390 | | | | _ | 395 | | | | | 400 |
| 20 | | | Ala | | 405 | | | | | 410 | _ | _ | | | 415 | |
| | | | Glu | 420 | | | | | 425 | | | | | 430 | | |
| 25 | | | 135 | | | | | 440 | | | | | 445 | | Ī | |
| 25 | | 450 | Ile | | | | 455 | | | | | 460 | | | - | |
| | 465 | | Leu | - | _ | 470 | | | | | 475 | | | | | 480 |
| 30 | | | Thr Ser | • | 485 | | | | | 490 | | | _ | | 495 | |
| | | | Met | 500 | | | | | 505 | | | | | 510 | | |
| 35 | | | 515 Ile | | | | | 520 | | | | | 525 | | | |
| | | 530 | Pro | | | | 535 | | | | | 540 | | _ | | |
| | 545 | | Asn | | | 550 | | | | | 555 | | | | | 560 |
| 40 | | | Trp | | 565 | | | | | 570 | | | | | 575 | |
| | | | Ala | 580 | - | | | _ | 585 | | | | | 590 | | _ |
| 45 | | | 595 Asp | | | | | 600 | | | _ | | 605 | | | |
| | | 610 | Ile | | | | 615 | | | | | 620 | | | | |
| | 625 Thr | Phe | Ser | Ser | Val | 630 Val | Glu | Leu | Ile | Asn | 635 His | Tyr | Arg | Asn | Glu | 640 Ser |
| 50 | Leu | Ala | Gln | Tyr | 645 Asn | Pro | Lys | Leu | Asp | 650 Val | Lys | Leu | Leu | Tyr | 655 Pro | Val |
| | Ser | Lys | Tyr | 660 Gln | Gln | Asp | Gln | | 665 Val | Lys | Glu | Asp | Asn | 670 Ile | Glu | Ala |
| 55 | Val | | 675 Lys | Lys | Leu | His | | 680 Tyr | Asn | Thr | Gln | | 685 Gln | Glu | Lys | Ser |
| | | 690 | • | | | | 695 | | | | | 700 | | | | |

| | | | | | | | | | | 98 | | | | | | | |
|----|-----------------------|--------------|-------------------------|--|-----------------------|------------------------|--------------------|--------------|--------------|------|----------------|------|------|------|-------------------|--------------|--|
| | | | | | | | | | | | | | | | | 1 Glu 720 | |
| | | | | | | | | | | | Phe | Asr | | | | Lys | |
| 5 | | | | | | | | | | | | | | | s Glu | Tyr | |
| | | | | | | | | | | | | | | Glr | n Arg | Ile | |
| 10 | | | | | | | | | | | | | Glu | Ile | | Asp | |
| | | | | | | | | | | | | | | | | Tyr 800 | |
| 15 | | | | Asp | | | | | | | | | | | | Gln | |
| ,, | | | | Thr 820 | | | | | | | | | | | | | |
| | | | | Lys | | | | | | | | | | | | | |
| 20 | | | | Ser | | | | | | | | | | | | | |
| | | | | Trp | | | | | | | | | | | | | |
| 25 | Leu Lvs | | | | | | | | | | | | | | | | |
| | Lys | | | | | | | | | | | | | | | | |
| | His Tvr | | | | | | | | | | | | | | | | |
| 30 | | | | | | | | | | | | | | | | | |
| | Thr 9 945 Pro V | | | | | | | | Ser | Leu | Asn 955 | Val | Thr | Leu | | Tyr 960 | |
| 35 | | | TYL. | | 965 | GIN . | Arg . | Arg | | | | | | | | | |
| | | | (2) | INFO | ORMA' | rion | FOR | SEQ | ID 1 | NO:5 | 0: | | | | | | |
| 40 | | | (A) 1 (B) 7 (C) 5 | QUENC LENGT FYPE : STRAN FOPOL | TH: 2 nuc IDEDN | 2160 :leic NESS: | base ac: sir | e pa: id | CS: irs | | | | | | | | |
| 45 | | (ii |) MC | LECU | LE 1 E: | YPE: | cDN | IA | | | | | | | | | |
| 50 | | | (B) | NAME LOCA OTHE | TION R IN | FORM | 21 ATIO | .57 N: | | | | | | | | | |
| | | | | QUEN | | | | | | | | | | | | | |
| 55 | ATG G Met Va | rg A al S | GC A er L | , | GC G ly G | AG G | AG C lu L | TG T eu P | TC A he T | hr G | GG G' ly Va | TG G | TG C | ro I | TC C le L 5 | TG eu | |

| | | | | | | 99 | | | | |
|----|---|---|---|-------------------|--|----|------|------|------|-----|
| | _ | _ | | GAC Asp | | | | | | 96 |
| 5 | | | | GCC Ala | | | | | | 144 |
| 10 | | | _ | CTG Leu | | | | | | 192 |
| 15 | | | | CAG Gln 70 | | | | | | 240 |
| 20 | | | | AAG Lys | | | | | | 288 |
| | | | | AAG Lys | | | | | | 336 |
| 25 | | | | GAC Asp | | | | | | 384 |
| 30 | | | | GAC Asp | | | | | | 432 |
| 35 | | | | AAC Asn 150 | | | | | | 480 |
| 40 | | | | TTC Phe | | | | | | 528 |
| 40 | _ | _ | | CAC His | | | | | | 576 |
| 45 | | | | GAC Asp | | | | | | 624 |
| 50 | | | | GAG Glu | | | | | | 672 |
| 55 | | | | ATC Ile 230 | | | | | | 720 |

| | 100 | |
|----|---|------|
| | GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG TCG TCC ATC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ser Ser Ile 245 250 255 | 768 |
| 5 | TTG CCA TTC ACG CCG CCA GTT GTG AAG AGA CTG CTG GGA TGG AAG AAG Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Gly Trp Lys Lys 260 265 270 | 816 |
| 10 | TCA GCT GGT GGG TCT GGA GGA GCA GGC GGA GGA GAG CAG AAT GGG CAG Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Glu Gln Asn Gly Gln 275 280 285 | 864 |
| 15 | GAA GAA AAG TGG TGT GAG AAA GCA GTG AAA AGT CTG GTG AAG AAG CTA Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu Val Lys Lys Leu 290 295 300 | 912 |
| 20 | AAG AAA ACA GGA CGA TTA GAT GAG CTT GAG AAA GCC ATC ACC ACT CAA Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln 305 310 315 320 | 960 |
| | AAC TGT AAT ACT AAA TGT GTT ACC ATA CCA AGC ACT TGC TCT GAA ATT Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr Cys Ser Glu Ile 325 330 335 | 1008 |
| 25 | TGG GGA CTG AGT ACA CCA AAT ACG ATA GAT CAG TGG GAT ACA ACA GGC Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp Asp Thr Thr Gly 340 345 350 | 1056 |
| 30 | CTT TAC AGC TTC TCT GAA CAA ACC AGG TCT CTT GAT GGT CGT CTC CAG Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp Gly Arg Leu Gln 355 360 365 | 1104 |
| 35 | 370 375 Hell Pro His Val Ile Tyr Cys Arg Leu Trp | 1152 |
| 40 | 385 390 395 Ala Ile Glu Asn | 1200 |
| | 405 410 Val Cys Val Asn Pro | 1248 |
| 45 | TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT CCA GTA TTA GTG Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro Pro Val Leu Val 420 425 430 | 1296 |
| 50 | CCC CGA CAC ACC GAG ATC CTA ACA GAA CTT CCG CCT CTG GAT GAC TAT Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro Leu Asp Asp Tyr 435 440 445 | .344 |
| 55 | ACT CAC TCC ATT CCA GAA AAC ACT AAC TTC CCA GCA GGA ATT GAG CCA Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala Gly Ile Glu Pro 450 450 460 | 392 |

| | | | | | | | 101 | | | | |
|----|---|---|-------------------|--|---|---|------|------|------|------------|------|
| | | | TAT Tyr | | | | | | | | 1440 |
| 5 | | | ACA Thr | | | | | | | | 1488 |
| 10 | | | GAA Glu 500 | | | | | | | | 1536 |
| 15 | | | CAG Gln | | | | | | | | 1584 |
| 20 | | | TAT Tyr | | | | | | | | 1632 |
| | | | TCA Ser | | | | | | | | 1680 |
| 25 | | | TGC Cys | | | _ | | | | | 1728 |
| 30 | _ | _ | ACA Thr 580 | | _ | | | | | | 1776 |
| 35 | | | GAA Glu | | | | | | | | 1824 |
| 40 | | | CCC Pro | | | | | | | | 1872 |
| 40 | | | ATT Ile | | | | | | | | 1920 |
| 45 | | | GCT Ala | | | | | | | GCC Ala | 1968 |
| 50 | | | CTA Leu 660 | | | | | | | | 2016 |
| 55 | | | GCA Ala | | | | | | | | 2064 |

| | | | | | | | | | | |)2 | | | | | | |
|----|--|--------------------|--------------|--------------------|-------|-------|---------------------|-------|--------------------|-------|-------|--------------------|------------|----------------|-------|------------------|------|
| E | | - 6 | 90 | | | | 6 | 95 | TA D | го Г | eu G | In T | rp L 00 | eu A | sp L | AA GTA ys Val | 2112 |
| 5 | Т Ъ 7 | TA A eu T 05 | CT C hr G | AG A' ln M | TG G | -, -, | CC C er P: 10 | CT T | CA G' er Va | TG C | rg C | GC T ys S 15 | CA A | GC A' er Me | rg ro | CA TAA er | 2160 |
| 10 | | | | (2) | INFO | RMAT | ON 1 | FOR S | SEQ] | ED NO | 0:51 | : | | | | | |
| 15 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 719 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | | | | | | | | | | | | | | | | |
| 20 | | | (V) | MOL FRAG SEQ | MENT | TYP | E: i | nter | ein nal N: S | EQ I | D NO | :51: | | | | | |
| 25 | | | l Se | r Ly | s Gl | y Gl | u Gl | u Le | u Ph | e Th | r Gl | y Va | | | | e Leu r Gly | |
| | | | | | | | | | | | | | | | | r Gly e Ile | |
| 30 | Су | 5 Th: | r Th | r Gly | , Lys | Let | 1 Pro | va: | l Pro | Tr | p Pro | o Thi | 45 Let | ı Va] | Thi | Thr | |
| | | | | | | | | | | | | | | | | Lys 80 Glu | |
| 35 | | | | | Phe | | | | Gly | y Asr | | | | | | Glu | |
| | Va1 | Lys | Phe 115 | Glu | Gly | Asp | Thr | Leu | Val | Asn | Arg | Ile | Glu | 110 Leu | Lys | Gly | |
| 40 | | | | | | | | Asn | Ile | | | | | Leu | | | |
| | | | | | | | | | Ile Arg | | | | | | | | |
| 45 | | | | Ala | | | | | Gln | | | | | | | | |
| | | | | | | | | | Tyr | | | | Gln | | | | |
| 50 | | | | | | | | Arg | Asp | | | | | | | | |
| | | | | | | | | | Gly | | | | | | | | |
| 55 | | | | | | | | | Ser Lys | | | | | | | | |
| | | | | 260 | | | | | 265 | | | | y | 270 | пур | nys | |

| | | | | | | | | | | 100 | | | | | | |
|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Ser | Ala | Gly 275 | Gly | Ser | Gly | Gly | Ala 280 | Gly | Gly | Gly | Glu | Gln 285 | Asn | Gly | Gln |
| | Glu | Glu 290 | ГÀЗ | Trp | Cys | Glu | Lys 295 | Ala | Val | Lys | Ser | Leu 300 | Val | Lys | Lys | Leu |
| 5 | Lys 305 | Lys | Thr | Gly | Arg | Leu 310 | Asp | Glu | Leu | Glu | Lys 315 | Ala | Ile | Thr | Thr | Gln 320 |
| | Asn | Cys | Asn | Thr | Lys 325 | Cys | Val | Thr | Ile | Pro 330 | Ser | Thr | Cys | Ser | Glu 335 | Ile |
| 10 | Trp | Gly | Leu | Ser 340 | Thr | Pro | Asn | Thr | Ile 345 | Asp | Gln | Trp | Asp | Thr 350 | Thr | Gly |
| | Leu | Tyr | Ser 355 | Phe | Ser | Glu | Gln | Thr 360 | Arg | Ser | Leu | Asp | Gly 365 | Arg | Leu | Gln |
| | Val | Ser 370 | His | Arg | Lys | Gly | Leu 375 | Pro | His | Val | Ile | Tyr 380 | Cys | Arg | Leu | Trp |
| 15 | Arg 385 | Trp | Pro | Asp | Leu | His 390 | Ser | His | His | Glu | Leu 395 | Lys | Ala | Ile | Glu | Asn 400 |
| | _ | | _ | | 405 | | | - | - | 410 | | | _ | Val | 415 | |
| 20 | _ | | _ | 420 | _ | | | | 425 | | | | | Val 430 | | |
| | | _ | 435 | | | | | 440 | | | | | 445 | Asp | _ | |
| 0.5 | | 450 | | | | | 455 | | | | | 460 | _ | Ile | | |
| 25 | 465 | | | _ | | 470 | | | | | 475 | - | - | Ile | | 480 |
| | _ | _ | | | 485 | | | | | 490 | | | | Asp | 495 | |
| 30 | | | | 500 | | | | | 505 | | | | | Asn 510 | | |
| | | - | 515 | | | | | 520 | | | | | 525 | Trp | | |
| 35 | | 530 | | | | | 535 | | | | | 540 | | Ser | | |
| 00 | 545 | | | | | 550 | | | | | 555 | | | Asn | | 560 |
| | | _ | | _ | 565 | _ | | | | 570 | | | _ | Leu | 575 | |
| 40 | | | | 580 | | | | | 585 | Ī | | | | 590 Ala | _ | |
| | | _ | 595 | | | | | 600 | _ | | | _ | 605 | Pro | | |
| 45 | Val | 610 Cys | Lys | Ile | Pro | Pro | 615 Gly | Cys | Asn | Leu | Lys | 620 Ile | Phe | Asn | Asn | Gln |
| | 625 Glu | Phe | Ala | Ala | Leu | 630 Leu | Ala | Gln | Ser | Val | 635 Asn | Gln | Gly | Phe | Glu | 640 Ala |
| | Val | Tyr | Gln | Leu | 645 Thr | Arg | Met | Cys | Thr | 650 Ile | Arg | Met | Ser | Phe | 655 Val | Lys |
| 50 | Gly | Trp | Gly | 660 Ala | Glu | Tyr | Arg | Arg | 665 Gln | Thr | Val | Thr | | 670 Thr | Pro | Cys |
| | Trp | | 675 Glu | Leu | His | Leu | | 680 Gly | Pro | Leu | Gln | _ | 685 Leu | Asp | Lys | Val |
| 55 | Leu 705 | 690 Thr | Gln | Met | Gly | | 695 Pro | Ser | Val | Arg | Cys 715 | 700 Ser | Ser | Met | Ser | |
| | ,05 | | | | | 710 | | | | | 113 | | | | | |

| | (2) INFORMATION FOR SEQ ID NO:52: | |
|----|--|-----|
| 5 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2421 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 10 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | |
| 15 | (A) NAME/KEY: Coding Sequence (B) LOCATION: 12418 (D) OTHER INFORMATION: | |
| 20 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52: ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15 | 48 |
| 25 | GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30 | 96 |
| 30 | GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45 | 144 |
| | TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60 | 192 |
| 35 | CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 80 | 240 |
| 40 | CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95 | 288 |
| 45 | CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG Arg Thr Ile Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110 | 336 |
| 50 | GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115 | 384 |
| | ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 140 | 432 |
| 55 | AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAC ASn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn | 480 |

| | | | | | | | 100 | | | | | | |
|----|-----|-------------------|--|-----|---|---|-----|-----|--|--|-----|------|-----|
| | 145 | | | 150 | | | | 155 | | | 160 | | |
| 5 | | ATC Ile | | | | | | | | | | 528 | ı |
| 10 | | CAG Gln | | | | | | | | | | 576 | |
| | | GTG Val | | | | | | | | | | 624 | |
| 15 | | AAA Lys 210 | | | | | | | | | | 672 | : |
| 20 | | ACC Thr | | | | | | | | | | 720 | H |
| 25 | _ | CTC Leu | | _ | _ | | | | | | | 768 | |
| 30 | | ATG Met | | | | | | | | | | 816 | ; |
| 30 | _ | GTG Val | | | | _ | | | | | | 864 | : |
| 35 | | GCA Ala 290 | | | | | | | | | | 912 | : |
| 40 | | GAT Asp | | | | | | | | | | 960 | , |
| 45 | | CCT Pro | | | | | | | | | | 1008 | 3 |
| 50 | | GTG Val | | | | | | | | | | 1056 | • |
| | | AGG Arg | | | | | | | | | | 1104 | ł |
| 55 | | CAG Gln | | | | | | | | | | 1152 | : 1 |

| | 370 | 375 | | 380 | |
|----|---|---------------------------------------|---------------------------------------|---|------|
| 5 | TAT CAC TAC GAA CGA Tyr His Tyr Glu Arg 385 | 390 | CCT GGA ATT (Pro Gly Ile 7 | GAT CTC TCA GGA TTA Asp Leu Ser Gly Leu 400 | 1200 |
| 10 | ACA CTG CAG AGT AAT Thr Leu Gln Ser Asn 405 | 110 561 | 410 | Val Lys Asp Glu Tyr 415 | 1248 |
| | GTG CAT GAC TTT GAG Val His Asp Phe Glu 420 | ory orn Pro | 425 | Thr Glu Gly His Ser 430 | 1296 |
| | ATT CAA ACC ATC CAG Ile Gln Thr Ile Gln 435 | 440 | ser Asn Arg A | la Ser Thr Glu Thr 445 | 1344 |
| 20 | TAC AGC ACC CCA GCT Tyr Ser Thr Pro Ala 450 | '455 | er Glu Se 40 | er Asn Ala Thr Ser 60 | 1392 |
| 25 | | 470 | al Ala Ser Th 475 | hr Ser Gln Pro Ala 480 | 1440 |
| 30 | AGT ATA CTG GGG GGC A Ser Ile Leu Gly Gly 5 485 | er ura ser G | 490 Leu Le | eu Gln Ile Ala Ser 495 | 1488 |
| | GGG CCT CAG CCA GGA C Gly Pro Gln Pro Gly G 500 | orn orn a | AT GGA TTT AC sn Gly Phe Th 05 | T GGT CAG CCA GCT r Gly Gln Pro Ala 510 | 1536 |
| 35 | ACT TAC CAT CAT AAC A Thr Tyr His His Asn S 515 | GC ACT ACC AC er Thr Thr Th 520 | CC TGG ACT GG | A AGT AGG ACT GCA y Ser Arg Thr Ala 525 | 1584 |
| 40 | CCA TAC ACA CCT AAT T Pro Tyr Thr Pro Asn L 530 | TG CCT CAC CA eu Pro His Hi 535 | AC CAA AAC GGG s Gln Asn Gly | y His Leu Gln His | 1632 |
| 45 | CAC CCG CCT ATG CCG CC His Pro Pro Met Pro Pr 545 | TO WIR LIG GI | A CAT TAC TGG y His Tyr Trp 555 | G CCT GTT CAC AAT O Pro Val His Asn 560 | 1680 |
| 50 | GAG CTT GCA TTC CAG CC Glu Leu Ala Phe Gln Pr 565 | T CCC ATT TC O Pro Ile Se | C AAT CAT CCT r Asn His Pro 570 | GCT CCT GAG TAT Ala Pro Glu Tyr 575 | 1728 |
| | TGG TGT TCC ATT GCT TA Trp Cys Ser Ile Ala Ty 580 | C TTT GAA ATO r Phe Glu Met 585 | - Asp Val Gln | | 1776 |
| 55 | TTT AAG GTT CCT TCA AG Phe Lys Val Pro Ser Se: | C TGC CCT ATT r Cys Pro Ile | GTT ACT GTT | | 1824 |
| | | | | | 106 |

107

| | | 595 | | | 600 | | | 605 | | | |
|----|---|-----|-------------------|-----|-----|------|--|-----|---|---|------|
| 5 | | | GGA Gly | | | | | | | | 1872 |
| 10 | | | GCC Ala | | | | | | | | 1920 |
| | - | | TGT Cys 645 | | | | | | | | 1968 |
| 15 | | | GTC Val | | | | | | | _ | 2016 |
| 20 | | _ | GGA Gly | | | | | | _ | | 2064 |
| 25 | | | GAT Asp | | | | | | | | 2112 |
| 30 | | | CAA Gln | | | | | | | | 2160 |
| | | | GGC Gly 725 | | | | | | | | 2208 |
| 35 | | | GCT Ala | | | | | | | | 2256 |
| 40 | | | ATG Met | | | | | | | | 2304 |
| 45 | | | AAA Lys | | | | | | | _ | 2352 |
| 50 | | | CTC Leu | | | | | | | | 2400 |
| | | | TTA Leu 805 | TGA | | | | | | | 2421 |

55 (2) INFORMATION FOR SEQ ID NO:53:

```
(i) SEQUENCE CHARACTERISTICS:
                (A) LENGTH: 806 amino acids
                (B) TYPE: amino acid
   5
                (C) STRANDEDNESS: single
                (D) TOPOLOGY: linear
              (ii) MOLECULE TYPE: protein
              (v) FRAGMENT TYPE: internal
  10
              (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
       Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
       Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
 15
                                      25
       Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                                  40
       Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
 20
                              55
       Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                           70
       Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
       Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 25
                                      105
       Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                 120
       Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
 30
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                         150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                         170
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
35
                                     185
      Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                             215
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                             235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                     245
                                         250
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
45
                 260
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
                                 280
     Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                             295
                                                 300
     Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                         310
     His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                                            315
                                         330
     Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
```

| | | | | | | | | | | .00 | | | | | | |
|-----|------------|------------|--------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Trp | Arg | Trp 355 | Pro | Asp | Leu | His | Lys 360 | Asn | Glu | Leu | Lys | His 365 | Val | ГÀЗ | Tyr |
| | Cys | Gln 370 | Tyr | Ala | Phe | Asp | Leu 375 | Lys | Cys | Asp | Ser | Val 380 | Сув | Val | Asn | Pro |
| 5 | Tyr 385 | His | Tyr | Glu | Arg | Val 390 | Val | Ser | Pro | Gly | Ile 395 | Asp | Leu | Ser | Gly | Leu 400 |
| | Thr | Leu | Gln | Ser | Asn 405 | Ala | Pro | Ser | Ser | Met 410 | Met | Val | Lys | Asp | Glu 415 | Tyr |
| 10 | Val | His | Asp | Phe 420 | Glu | Gly | Gln | Pro | Ser 425 | Leu | Ser | Thr | Glu | Gly 430 | His | Ser |
| | | | 435 | Ile | | | | 440 | | | | | 445 | | | |
| | Tyr | Ser 450 | Thr | Pro | Ala | Leu | Leu 455 | Ala | Pro | Ser | Glu | Ser 460 | Asn | Ala | Thr | Ser |
| 15 | Thr 465 | Ala | naA | Phe | Pro | Asn 470 | Ile | Pro | Val | Ala | Ser 475 | Thr | Ser | Gln | Pro | Ala 480 |
| | Ser | Ile | Leu | Gly | Gly 485 | Ser | His | Ser | Glu | Gly 490 | | Leu | Gln | Ile | Ala 495 | |
| 20 | | | | Pro 500 | | | | | 505 | _ | | | - | 510 | | |
| | Thr | Tyr | His 515 | His | Asn | Ser | Thr | Thr 520 | Thr | Trp | Thr | Gly | Ser 525 | Arg | Thr | Ala |
| | Pro | Tyr 530 | Thr | Pro | Asn | Leu | Pro 535 | His | His | Gln | Asn | Gly 540 | His | Leu | Gln | His |
| 25 | His 545 | Pro | Pro | Met | Pro | Pro 550 | His | Pro | Gly | His | Tyr 555 | Trp | Pro | Val | His | Asn 560 |
| | Glu | Leu | Ala | Phe | Gln 565 | Pro | Pro | Ile | Ser | Asn 570 | His | Pro | Ala | Pro | Glu 575 | Tyr |
| 30 | Trp | Cys | Ser | Ile 580 | Ala | Tyr | Phe | Glu | Met 585 | Asp | Val | Gln | Val | Gly 590 | Glu | Thr |
| | | | 5 9 5 | Pro | | | • | 600 | | | | | 605 | _ | • | |
| 0.5 | | 610 | | Gly | | | 615 | | _ | | • | 620 | | | | |
| 35 | H15 | Arg | Thr | Glu | Ala | 630 | Glu | Arg | Ala | Arg | Leu 635 | His | Ile | Gly | Lys | Gly 640 |
| | | | | Glu | 645 | | | | | 650 | | | | | 655 | |
| 40 | | | | Ala 660 | | | | | 665 | | | | | 670 | | |
| | Gly | Arg | Ala 675 | Pro | Gly | Asp | Ala | Val 680 | His | Lys | Ile | Tyr | Pro 685 | Ser | Ala | Tyr |
| | | 690 | | Phe | | | 695 | | - | | _ | 700 | | | | |
| 45 | Ala 705 | Ala | Thr | Ala | Gln | Ala 710 | Ala | Ala | Ala | Ala | Gln 715 | Ala | Ala | Ala | Val | Ala 720 |
| | | | | Pro | 725 | | | | | 730 | | | | | 735 | |
| 50 | | | | Ala 740 | | | | | 745 | | | | | 750 | | |
| | | | 755 | Arg | | | | 760 | | | | | 765 | | | |
| | | 770 | | Ile | | | 775 | | | | | 780 | | | | |
| 55 | Arg 785 | Ala | Leu | Gln | Leu | Leu 790 | Asp | Glu | Val | Leu | His 795 | Thr | Met | Pro | Ile | Ala 800 |

110

Asp Pro Gln Pro Leu Asp 805

| 5 | (2) INFORMATION FOR SEQ ID NO:54: | |
|-----|---|-----|
| 10 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3120 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 15 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | |
| 13 | (A) NAME/KEY: Coding Sequence(B) LOCATION: 13117(D) OTHER INFORMATION: | |
| 20 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54: | |
| 0.5 | ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 | 48 |
| 25 | GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 | 96 |
| 30 | GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 | 144 |
| 35 | TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60 | 192 |
| 40 | CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 80 | 240 |
| | CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95 | 288 |
| 45 | CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110 | 336 |
| 50 | GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115 | 384 |
| 55 | ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 140 | 432 |

| | | | | | | | 111 | | | | |
|----|---|---|-------------------|---|---|--|-----|--|--|--|------|
| | | | AAC Asn | | | | | | | | 480 |
| 5 | | | AAG Lys | | | | | | | | 528 |
| 10 | | | CTC Leu | | | | | | | | 576 |
| 15 | | | CTG Leu 195 | | | | | | | | 624 |
| 20 | | | GAC Asp | | _ | | | | | | 672 |
| 20 | | | GCC Ala | | | | | | | | 720 |
| 25 | | | AGA Arg | | | | | | | | 768 |
| 30 | | | GCG Ala | | | | | | | | 816 |
| 35 | _ | _ | GTC Val 275 | _ | | | | | | | 864 |
| 40 | | _ | ATT Ile | | | | | | | | 912 |
| 40 | | | GAG Glu | | | | | | | | 960 |
| 45 | | | GAA Glu | | | | | | | | 1008 |
| 50 | | | CTC Leu | | | | | | | | 1056 |
| 55 | | | CGG Arg 355 | _ | | | | | | | 1104 |

| | | | | | | | | | | | | 4 | | | | | | | | |
|----|-------------------|-------------------|-------------------|-------------------|--------------------|--------------|--------------------|--------------|------------|-------------------|-------------------|-----------------|--------------|----------------------|------------|--------------------|----------------|----------------|-----------------------|------|
| | | 3 | 70 | . | | | 110 | 375 | ; ; | у 1. | re r | eu | Val | As ₁ | o Al | a M | et | Se: | C CAG r Gln | 1152 |
| 5 | 38 | 5 | | | | | 390 | GIII | 1 111. | I Pr | ie G. | Iu (| G1u 395 | Let | ı Ar | g L | eu | Va: | C ACG l Thr 400 | 1200 |
| 10 | CA Gl | G GA | AC A Sp T | CA G hr G | | AT (sn (| GAG Glu | CTG Leu | Lys | G AA s Ly | A C | eu (| CAG Gln | CAC Glr | AC' | T C | ln | GAC Glu | TAC Tyr | 1248 |
| 15 | TT(Pho | C Al | C A | | AG T ln T 20 | AC o | CAG Sln | GAG Glu | AG(| C CT Le 42 | u Ar | eg 1 | ATC Ile | CAA Gln | GC: Ala | r ca a Gl 43 | n | TTI Phe | GCC Ala | 1296 |
| 20 | | | 43 | 15 | | - L | CI , | FIO | 440 | i Gi | ı Ar | gL | eu | Ser | Arc 445 | g Gl | u : | Thr | GCC Ala | 1344 |
| | CTC | CA G1 45 | G CA n Gl 0 | G AA .n Ly | G CA | AG G Ln V | u1 . | CT Ser | CTG Leu | GA0 | G GC | C T a T | rp | TTG Leu 460 | CAG Gln | CG Ar | T (| GAG Glu | GCA Ala | 1392 |
| 25 | CAG Gln 465 | AC. | A CT r Le | G CA u Gl | G CA n Gl | ··· · | AC C yr A 70 | GC .rg | GTG Val | GAC Glu | CTO | u A | CC (la (| GAG Glu | AAG Lys | CA Hi | C C | AG 31n | AAG Lys 480 | 1440 |
| 30 | ACC Thr | CTO | G CA | G CT | G CT u Le 48 | u // | GG A | AG ys | CAG Gln | CAG Gln | AC(Thi | r I. | TC 1 | ATC Ile | CTG Leu | GA: Ası | A | AC sp 95 | GAG Glu | 1488 |
| 35 | CTG Leu | ATC Ile | CAC | TGG Trj 500 | , | G CC | G C | GG (rg (| CAG Gln | CAG Gln 505 | CTC | G GC | CC C | GG Gly | AAC Asn | GGC Gly 510 | G. | GG ly | CCC Pro | 1536 |
| 40 | | | 515 | | | - AD | p v | 2 I | 520 | GIN | ser | Tr | ърС | ys | Glu 525 | Lys | Le | eu . | Ala | 1584 |
| | GAG Glu | ATC Ile 530 | ATO | TGC Trp | Glr | 3 AA 1 As | C CC n Ai 53 | .y c | CAG Sln | CAG Gln | ATC Ile | CG Ar | g A | .GG (.rg / 40 | GCT Ala | GAG Glu | C# Hi | AC (| CTC Leu | 1632 |
| 45 | TGC Cys 545 | CAG Gln | CAG Gln | CTG | Pro | 110 550 | S PI | C G | GC ly | CCA Pro | GTG Val | GA Gl: 55 | u G | AG A lu N | ATG Met | CTG Leu | GC Al | .a (| GAG Glu G60 | 1680 |
| 50 | GTC . Val . | AAC Asn | GCC Ala | ACC Thr | ATC Ile 565 | | G GA | C A p I | TT / | тте | TCA Ser 570 | GC0 Ala | C C | rg c eu V | TG / | ACC Thr | AG Se 57 | r 1 | ACA Thr | 1728 |
| 55 | TTC ; | ATC Ile | ATT Ile | GAG Glu 580 | AAG Lys | CAC Glr | CC Pr | T C | ro c | CAG 31n 585 | GTC Val | CT(| ı Ly | AG A /s T | hr (| CAG Gln 590 | AC Th | C A | AG ys | 1776 |

| | | | | | | 113 | | | | |
|----|--|-------------------|--|--|--|-----|--|--|--|------|
| | | GCC Ala 595 | | | | | | | | 1824 |
| 5 | | CCC Pro | | | | | | | | 1872 |
| 10 | | CTG Leu | | | | | | | | 1920 |
| 15 | | AAC Asn | | | | | | | | 1968 |
| 20 | | GCC Ala | | | | | | | | 2016 |
| | | CGG Arg 675 | | | | | | | | 2064 |
| 25 | | TCT Ser | | | | | | | | 2112 |
| 30 | | CTG Leu | | | | | | | | 2160 |
| 35 | | GCC Ala | | | | | | | | 2208 |
| 40 | | GTG Val | | | | | | | | 2256 |
| 40 | | GCG Ala 755 | | | | | | | | 2304 |
| 45 | | ACC Thr | | | | | | | | 2352 |
| 50 | | AGC Ser | | | | | | | | 2400 |
| 55 | | TTC Phe | | | | | | | | 2448 |

| | | | | | | | | | 114 | | | | | | | |
|----|----------------------------|---------------------|----------------------|-----------------------|-----------------------|-----------------------|-------------------|-------------------|-------------------|------------------------------|-----------------------|-------------------|--------------|-------------------|-------------------|------|
| | CAG 7 | rgg T Trp P | TT GA he As | F | GTG Val | ATG Met | GAG Glu | GTC Val 825 | L Let | AAG Lys | AAG Lys | CAC His | CAC His | Ly | G CCC s Pro | 2496 |
| 5 | CAC T His T | - | AT GA sn As 35 | T GGG p Gly | GCC Ala | ATC Ile | CTA Leu 840 | GIY | TTT Phe | GTG Val | AAT Asn | AAG Lys 845 | CAA Gln | CAC Glr | G GCC | 2544 |
| 10 | CAC G His A 8 | AC C'sp Le | TG CT eu Le | C ATC u Ile | AAC Asn | AAG Lys 855 | CCC Pro | GAC Asp | GGG | ACC Thr | TTC Phe 860 | TTG Leu | TTG Leu | CGC | TTT Phe | 2592 |
| 15 | AGT G. Ser A. 865 | AC TO | CA GA | A ATC | GGG Gly 870 | GGC Gly | ATC Ile | ACC Thr | ATC Ile | GCC Ala 875 | TGG Trp | AAG Lys | TTT Phe | GAC Asp | TCC Ser 880 | 2640 |
| 20 | CCG G | AA CG lu Ar | GC AAG | C CTG Leu 885 | TGG Trp | AAC Asn | CTG Leu | AAA Lys | CCA Pro 890 | TTC Phe | ACC Thr | ACG Thr | CGG Arg | GAT Asp 895 | TTC Phe | 2688 |
| | TCC AT | | 900 |) | AIG . | ASP . | Arg | ьец 905 | Gly | Asp | Leu . | Ser ' | Tyr 910 | Leu | Ile | 2736 |
| 25 | TAT GT Tyr Va | 91 | 5 | | nig . | : | 920 | Asp | Glu | Val : | Phe s | Ser 1 925 | ГЛЗ | Tyr | Tyr | 2784 |
| 30 | ACT CC Thr Pr 93 | T GTO O Val O | G CTG l Leu | GCT Ala | Lys A | GCT (Ala V 935 | GTT (/al / | GAT Asp | GGA Gly | Tyr V | GTG / Val I 940 | AAA C | CCA Pro | CAG Gln | ATC Ile | 2832 |
| 35 | AAG CA Lys Gl: 945 | A GTO | GTC Val | | GAG 1 Glu F 950 | TT C | TG 1 | AAT (| Ala : | TCT (Ser <i>I</i> 955 | GCA G | AT G | CT (| Gly | GGC Gly 960 | 2880 |
| 40 | AGC AGG Ser Sei | C GCC r Ala | ACG Thr | TAC I Tyr 1 965 | ATG G Met A | SAC C | AG C | иа в | CCC : Pro s | CC C | CCA G | CT G la V | al (| rgc Cys 975 | CCC Pro | 2928 |
| | CAG GCT Gln Ala | | 980 | | 1 | YL P | 9 | 85 | Asn F | ro A | sp H | is V. 9: | al I 90 | eu i | Asp | 2976 |
| 45 | CAG GAT Gln Asp | GGA Gly 995 | GAA Glu | TTC G | SAC C | TG G eu A | sp G | AG A lu T | CC A | TG G | AT G' sp Va | al Al | CC A la A | .GG (| CAC His | 3024 |
| 50 | GTG GAG Val Glu 1010 | GAA Glu | CTC | TTA C Leu A | GC CC rg Ai | 9 1 | CA A | TG G et A | AC A sp S | GT C er Le | eu As | AC TO | CC C | GC C rg I | CTC Jeu | 3072 |
| 55 | TCG CCC Ser Pro 1025 | CCT Pro | GCC (| GGT C Gly L | Cu Fi | CC AC | C TO | CT G | CC Ac | rg G] | GC TC ly Se | C CI | C T | CA Ter | 'GA | 3120 |

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(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1039 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein

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55

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

| | | (2 | ~1, . |)EQUI | SIVCE | DESC | LKIP. | LION | | ע גע | 110 | ٠. | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 15 | Met 1 | Val | Ser | Lys | Gly 5 | Glu | Glu | Leu | Phe | Thr 10 | Gly | Val | Val | Pro | Ile 15 | Leu |
| | Val | Glu | Leu | Asp 20 | Gly | Asp | Val | Asn | Gly 25 | His | Lys | Phe | Ser | Val 30 | Ser | Gly |
| 20 | Glu | Gly | Glu 35 | Gly | Asp | Ala | Thr | Tyr 40 | Gly | Lys | Leu | Thr | Leu 45 | Lys | Phe | Ile |
| | Суз | Thr 50 | Thr | Gly | Lys | Leu | Pro 55 | Val | Pro | Trp | Pro | Thr 60 | Leu | Val | Thr | Thr |
| | Leu 65 | Thr | Tyr | Gly | Val | Gln 70 | Cys | Phe | Ser | Arg | Tyr 75 | Pro | Asp | His | Met | Lys 80 |
| 25 | Gln | His | Asp | Phe | Phe 85 | Lys | Ser | Ala | Met | Pro 90 | Glu | Gly | Tyr | Val | Gln 95 | Glu |
| | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | Asn | Tyr | Lys | Thr | Arg 110 | Ala | Glu |
| 30 | Val | Lys | Phe 115 | Glu | Gly | Asp | Thr | Leu 120 | Val | Asn | Arg | Ile | Glu 125 | Leu | Lys | Gly |
| | Ile | Asp 130 | Phe | Lys | Glu | Asp | Gly 135 | Asn | Ile | Leu | Gly | His 140 | Lys | Leu | Glu | Tyr |
| | Asn 145 | Tyr | Asn | Ser | His | Asn 150 | Val | Tyr | Ile | Met | Ala 155 | Asp | Lys | Gln | Lys | Asn 160 |
| 35 | Gly | Ile | Lys | Val | Asn 165 | Phe | Lys | Ile | Arg | His 170 | Asn | Ile | Glu | Asp | Gly 175 | Ser |
| | Val | Gln | Leu | Ala 180 | Asp | His | Tyr | Gln | Gln 185 | Asn | Thr | Pro | Ile | Gly 190 | Asp | Gly |
| 40 | Pro | Val | Leu 195 | Leu | Pro | Asp | Asn | His 200 | Tyr | Leu | Ser | Thr | Gln 205 | Ser | Ala | Leu |
| | Ser | Lys 210 | Asp | Pro | Asn | Glu | Lys 215 | Arg | qaA | His | Met | Val 220 | Leu | Leu | Glu | Phe |
| | Val 225 | Thr | Ala | Ala | Gly | 11e 230 | Thr | Leu | Gly | Met | Asp 235 | Glu | Leu | Tyr | Lys | Ser 240 |
| 45 | Gly | Leu | Arg | Ser | Thr 245 | Met | Ala | Gly | Trp | Ile 250 | Gln | Ala | Gln | Gln | Leu 255 | Gln |
| | Gly | qaA | Ala | Leu 260 | Arg | Gln | Met | Gln | Val 265 | Leu | Tyr | Gly | Gln | His 270 | Phe | Pro |
| 50 | Ile | Glu | Val 275 | Arg | His | Tyr | Leu | Ala 280 | Gln | Trp | Ile | Glu | Ser 285 | Gln | Pro | Trp |
| | Asp | Ala 290 | Ile | Asp | Leu | Asp | Asn 295 | Pro | Gln | Asp | Arg | Ala 300 | Gln | Ala | Thr | Gln |
| | Leu | Leu | Glu | Glv | Leu | Val | Gln | Glu | Len | Gln | Lvs | Lvs | Ala | Glu | His | Gln |

115

335

Leu Leu Glu Gly Leu Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln

Val Gly Glu Asp Gly Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala

315

330

310

| | 116 | |
|-----|--|---|
| | Thr Gln Leu Gln Lys Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg | |
| | 340 345 350 Cys Ile Arg His Ile Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala | 3 |
| 5 | 355 360 365 | а |
| | 370 375 Ser Ser Pro Ala Gly Ile Leu Val Asp Ala Met Ser Glr | 1 |
| | Lys His Leu Gln Ile Asn Gln Thr Phe Glu Glu Leu Arg Leu Val The | _ |
| 10 | Gln Asp Thr Glu Asp Glu Leu Lyg Lyg 1395 |) |
| 10 | 405 410 415 | • |
| | Phe Ile Ile Gln Tyr Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala 420 425 | |
| | Gln Leu Ala Gln Leu Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala 435 440 | |
| 15 | Leu Gln Gln Lys Gln Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala 450 455 | |
| | Gln Thr Leu Gln Gln Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys 465 470 | |
| | 465 470 475 480 | |
| 20 | Thr Leu Gln Leu Leu Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu 485 490 | |
| | Leu lie Gin Trp Lys Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro | |
| | Pro Glu Gly Ser Leu Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala | |
| 25 | Glu Ile Ile Trp Gln Asn Arg Gln Gln Ile Arg Arg Ala Glu His Leu | |
| | 530 535 540 Cys Gln Gln Leu Pro Ille Pr | |
| | Cys Gln Gln Leu Pro Ile Pro Gly Pro Val Glu Glu Met Leu Ala Glu 545 550 555 | |
| 30 | Val Asn Ala Thr Ile Thr Asp Ile Ile Ser Ala Leu Val Thr Ser Thr | |
| | Phe Ile Ile Glu Lys Gln Pro Pro Gln Val Leu Lys Thr Gln Thr Lys | |
| | Phe Ala Ala Thr Val Arg Leu Leu Val Gly Gly Lys Leu Asn Val His | |
| 35 | 595 600 Het Asn Pro Pro Gln Val Lus 10 605 | |
| | Met Asn Pro Pro Gln Val Lys Ala Thr Ile Ile Ser Glu Gln Gln Ala 610 615 620 | |
| | Lys Ser Leu Leu Lys Asn Glu Asn Thr Arg Asn Glu Cys Ser Gly Glu | |
| 40 | Ile Leu Asn Asn Cys Cys Val Met Glu Tyr His Gln Ala Thr Gly Thr | |
| | Leu Ser Ala His Phe Arg Asn Met Ser Leu Lys Arg Ile Lys Arg Ala | |
| | Asp Arg Arg Gly Ala Gly Con Val | |
| 45 | Asp Arg Arg Gly Ala Glu Ser Val Thr Glu Glu Lys Phe Thr Val Leu 675 680 685 | |
| | Phe Glu Ser Gln Phe Ser Val Gly Ser Asn Glu Leu Val Phe Gln Val 690 695 | |
| | Lys Thr Leu Ser Leu Pro Val Val Val Ile Val His Gly Ser Glr Nor | |
| 50 | His Asn Ala Thr Ala Thr Val Leu Trp Asp Asn Ala Phe Ala Glu Pro | |
| 50 | 725 730 735 Gly Arg Val Pro Phe Ala Val Pro Pro 735 | |
| | Gly Arg Val Pro Phe Ala Val Pro Asp Lys Val Leu Trp Pro Gln Leu 740 745 750 | |
| e e | Cys Glu Ala Leu Asn Met Lys Phe Lys Ala Glu Val Gln Ser Asn Arg 755 760 | |
| 55 | Gly Leu Thr Lys Glu Asn Leu Val Phe Leu Ala Gln Lys Leu Phe Asn | |
| | 775 780 | |

117

| | | | | | | | | | | 117 | | | | | | | |
|----|------------|------------------|------------|------------|-----------------------|-------------|-------------|-------------|------------|------------|-------------|-------------|------------|------------|------------|------------|----|
| | Asn 785 | Ser | Ser | Ser | His | Leu 790 | Glu | Asp | туr | Ser | Gly 795 | Leu | Ser | Val | Ser | Trp 800 | |
| | Ser | Gln | Phe | Asn | Arg 805 | Glu | Asn | Leu | Pro | Gly 810 | Trp | Asn | Tyr | Thr | Phe 815 | Trp | |
| 5 | Gln | Trp | Phe | Asp 820 | Gly | Val | Met | Glu | Val 825 | Leu | Lys | Lys | His | His 830 | Lys | Pro | |
| | His | Trp | Asn 835 | Asp | Gly | Ala | Ile | Leu 840 | Gly | Phe | Val | Asn | Lys 845 | Gln | Gln | Ala | |
| 10 | His | Asp 850 | Leu | Leu | Ile | Asn | Lys 855 | Pro | Asp | Gly | Thr | Phe 860 | Leu | Leu | Arg | Phe | |
| | Ser 865 | Asp _. | Ser | Glu | Ile | Gly 870 | Gly | Ile | Thr | Ile | Ala 875 | Trp | Lys | Phe | Asp | Ser 880 | |
| | Pro | Glu | Arg | Asn | Leu 885 | Trp | Asn | Leu | Lys | Pro 890 | Phe | Thr | Thr | Arg | Asp 895 | Phe | |
| 15 | Ser | Ile | Arg | Ser 900 | Leu | Ala | Asp | Arg | Leu 905 | Gly | Asp | Leu | Ser | Tyr 910 | Leu | Ile | |
| | Tyr | Val | Phe 915 | Pro | Asp | Arg | Pro | Lys 920 | Asp | Glu | Val | Phe | Ser 925 | Lys | Tyr | Tyr | |
| 20 | Thr | Pro 930 | Val | Leu | Ala | Lys | Ala 935 | Val | Asp | Gly | Tyr | Val 940 | Lys | Pro | Gln | Ile | |
| | Lys 945 | Gln | Val | Val | Pro | Glu 950 | Phe | Val | Asn | Ala | Ser 955 | Ala | Asp | Ala | Gly | Gly 960 | |
| | Ser | Ser | Ala | Thr | Tyr 965 | Met | Asp | Gln | Ala | Pro 970 | Ser | Pro | Ala | Val | Cys 975 | Pro | |
| 25 | Gln | Ala | Pro | Tyr 980 | Asn | Met | Tyr | Pro | Gln 985 | Asn | Pro | Asp | His | Val 990 | Leu | Asp | |
| | Gln | Asp | Gly 995 | Glu | Phe | qaA | | Asp 1000 | Glu | Thr | Met | | Val | Ala | Arg | His | |
| 30 | | Glu 1010 | Glu | Leu | Leu | _ | Arg 1015 | Pro | Met | Asp | | Leu 1020 | Asp | Ser | Arg | Leu | |
| | Ser 025 | Pro | Pro | Ala | Gly | Leu 1030 | Phe | Thr | Ser | | Arg 1035 | Gly | Ser | Leu | | ı | |
| | | | (2) |) IN | FORM | OITA | v FOI | R SE | Q ID | NO: | 56: | | | | | | |
| 35 | | (: | i) SI | EQUEI | NCE (| CHARA | ACTE | RIST: | ICS: | | | | | | | | |
| | | | | | GTH: E: ni | | | - | airs | | | | | | | | |
| 40 | | | | | ANDEI OLOG | | | _ | е | | | | | | | | |
| | | (: | ii) r | MOLE | CULE | TYPI | E: cl | DNA | | | | | | • | | | |
| | | (: | ix) 1 | FEAT | URE: | | | | | | | | | | | | |
| 45 | | | (B) | LO | ME/KI CATIO HER | : NC | 1: | 1872 | equei | nce | | | | | | | |
| 50 | | (2 | ki) S | SEQUI | ENCE | DES | CRIP | гіои | : SE | Q ID | ио: | 56: | | | | | |
| 50 | | | | | GCG Ala 5 | | | | | | | | | | | | 48 |
| | | | | | | | | | | | | | | | | | |

96

GGA ACT GCT GGG GTC GTC CCG GTG GTC CCC GGG GAG GTG GAG GTG GTG

Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val

| | 118 | |
|----|---|-----|
| | 20 25 30 | |
| 5 | AAG GGG CAG CCA TTC GAT GTG GGC CCA CGC TAC ACG CAG CTG CAG TAC Lys Gly Gln Pro Phe Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr 35 40 45 | 144 |
| 10 | ATC GGC GAG GGC GCG TAC GGC ATG GTC AGC TCA GCT TAT GAC CAC GTG Ile Gly Glu Gly Ala Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val 50 55 60 | 192 |
| 45 | CGC AAG ACC AGA GTG GCC ATC AAG AAG ATC AGC CCC TTT GAG CAT CAA Arg Lys Thr Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln 65 70 75 80 | 240 |
| 15 | ACC TAC TGT CAG CGC ACG CTG AGG GAG ATC CAG ATC TTG CTG CGA TTC Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe 85 90 95 | 288 |
| 20 | CGC CAT GAG AAT GTT ATA GGC ATC CGA GAC ATC CTC AGA GCG CCC ACC Arg His Glu Asn Val Ile Gly Ile Arg Asp Ile Leu Arg Ala Pro Thr 105 110 | 336 |
| 25 | CTG GAA GCC ATG AGA GAT GTT TAC ATT GTT CAG GAC CTC ATG GAG ACA Leu Glu Ala Met Arg Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr 115 120 125 | 384 |
| 30 | GAC CTG TAC AAG CTG CTT AAA AGC CAG CAG CTG AGC AAT GAC CAC ATC Asp Leu Tyr Lys Leu Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile 130 135 140 | 432 |
| 35 | TGC TAC TTC CTC TAC CAG ATC CTC CGG GGC CTC AAG TAT ATA CAC TCA Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser 150 155 160 | 480 |
| 33 | GCC AAT GTG CTG CAC CGG GAC CTG AAG CCT TCC AAT CTG CTT ATC AAC Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn 165 170 175 | 528 |
| 40 | ACC ACC TGC GAC CTT AAG ATC TGT GAT TTT GGC CTG GCC CGG ATT GCT Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala 180 185 190 | 576 |
| 45 | GAC CCT GAG CAC GAC CAC ACT GGC TTT CTG ACG GAG TAT GTG GCC ACA Asp Pro Glu His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr 195 200 205 | 624 |
| 50 | CGC TGG TAC CGA GCC CCA GAG ATC ATG CTT AAT TCC AAG GGC TAC ACC Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr 210 215 220 | 672 |
| | AAA TCC ATC GAC ATC TGG TCT GTG GGC TGC ATT CTG GCT GAG ATG CTC Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu 235 240 | 720 |
| 55 | TCC AAC CGG CCC ATC TTC CCC GGC AAG CAC TAC CTG GAC CAG CTC AAC Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn | 768 |

| | | | | | | | | | | 119 | | | | | | | | |
|----|------------|------------|------------|------------|-------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------|---|
| | | | | | 245 | | | | | 250 | | | | | 255 | | | |
| 5 | | | | | ATC Ile | | | | | | | | | | | | 816 | |
| 10 | | | | | AAG Lys | | | | | | | | | | | | 864 | |
| | | | _ | _ | TGG Trp | | | | | | | | | | | | 912 | |
| 15 | | | | | GAC Asp | | | | | | | | | | | | 960 | |
| 20 | | | | | GCG Ala 325 | | | | | | | | | | | | 1008 | |
| 25 | | | | | CCA Pro | | | | | | | | | | | | 1056 | |
| 30 | | | | | CCC Pro | | | | | | | | | | | | 1104 | |
| | | | | | CAG Gln | | | | | | | | | | | | 1152 | |
| 35 | | | | | GAA Glu | | | | | | | | | | | | 1200 | |
| 40 | | | | | GTT Val 405 | | | | | | | | | | | | 1248 | |
| 45 | | | | | ACA Thr | | | | | | | | | | | | 1296 | |
| 50 | | | | | CCT Pro | | | | | | | | | | | | 1344 | |
| | | | | | TGC Cys | | | | | | | | | | | | 1392 | |
| 55 | GAC Asp | TTT Phe | TTC Phe | AAG Lys | AGT Ser | GCC Ala | ATG Met | CCC Pro | GAA Glu | GGT Gly | TAT Tyr | GTA Val | CAG Gln | GAA Glu | AGA Arg | ACT Thr | 1440 | 1 |

| | 465 470 475 | |
|----|--|------|
| | 4/5 480 | |
| 5 | 485 490 495 | 1488 |
| 10 | TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA GGT ATT GAT Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp 500 510 | 1536 |
| | TTT AAA GAA GAT GGA AAC ATT CTT GGA CAC AAA ATG GAA TAC AAT TAT Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met Glu Tyr Asn Tyr 515 520 525 | 1584 |
| 15 | AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA AAG AAT GGC ATC Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro Lys Asn Gly Ile 530 535 540 | 1632 |
| 20 | AAA GTT AAC TTC AAA ATT AGA CAC AAC ATT AAA GAT GGA AGC GTT CAA Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp Gly Ser Val Gln 545 550 555 | 1680 |
| 25 | TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT GGC CCT GTC Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val 565 570 575 | 1728 |
| 30 | CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC CTT TCC AAA Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys 580 585 590 | 1776 |
| | GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG TTT GTA ACA Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu Phe Val Thr 595 600 605 | 1824 |
| 35 | GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA CCT CAG GAG T Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys Pro Gln Glu 610 620 | 1873 |
| 40 | AA (2) INFORMATION FOR SEQ ID NO:57: | 1875 |
| 45 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 624 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 50 | (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal | |
| 55 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:57: Met Ala Ala Ala Ala Ala Pro Gly Gly Gly Gly Glu Pro Arg 1 5 10 15 Gly Thr Ala Gly Val Val Pro Val Val Pro Gly Glu Val Glu Val Val | |

| | | | | 20 | | | | | 25 | | | | | 30 | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Lys | Gly | Gln 35 | Pro | Phe | Asp | Val | Gly 40 | Pro | Arg | Tyr | Thr | Gln 45 | Leu | Gln | Tyr |
| 5 | Ile | Gly 50 | Glu | Gly | Ala | Tyr | Gly 55 | Met | Val | Ser | Ser | Ala 60 | Tyr | Asp | His | Val |
| | Arg 65 | Lys | Thr | Arg | Val | Ala 70 | Ile | Lys | Lys | Ile | Ser 75 | Pro | Phe | Glu | His | Gln 80 |
| | Thr | Tyr | Cys | Gln | Arg 85 | Thr | Leu | Arg | Glu | Ile 90 | Gln | Ile | Leu | Leu | Arg 95 | Phe |
| 10 | Arg | His | Glu | Asn 100 | Val | Ile | Gly | Ile | Arg 105 | Asp | Ile | Leu | Arg | Ala 110 | Pro | Thr |
| | Leu | Glu | Ala 115 | Met | Arg | Asp | Val | Tyr 120 | Ile | Val | Gln | Asp | Leu 125 | Met | Glu | Thr |
| 15 | Asp | Leu 130 | Tyr | Lys | Leu | Leu | Lys 135 | Ser | Gln | Gln | Leu | Ser 140 | Asn | Asp | His | Ile |
| | Cys 145 | Tyr | Phe | Leu | Tyr | Gln 150 | Ile | Leu | Arg | Gly | Leu 155 | Lys | Tyr | Ile | His | Ser 160 |
| | Ala | Asn | Val | Leu | His 165 | Arg | Asp | Leu | Lys | Pro 170 | Ser | Asn | Leu | Leu | Ile 175 | Asn |
| 20 | | | | 180 | Leu | _ | | | 185 | | - | | | 190 | | |
| | | | 195 | | Asp | | | 200 | | | | | 205 | | | |
| 25 | | 210 | | | Ala | | 215 | | | | | 220 | | | | |
| | 225 | | | | Ile | 230 | | | | | 235 | | | | | 240 |
| 20 | | | | | Ile 245 | | | | | 250 | | | | | 255 | |
| 30 | | | | 260 | Ile | | | | 265 | | | | | 270 | | |
| | | | 275 | | Lys | | | 280 | | | | | 285 | | | |
| 35 | | 290 | | | Trp | | 295 | | | | | 300 | | | | |
| | 305 | | | | Asp Ala | 310 | | | | | 315 | | | | | 320 |
| 40 | | | | | 325 Pro | | | | | 330 | | | | | 335 | |
| 40 | | | | 340 | Pro | | | | 345 | | | | | 350 | | |
| | | | 355 | | Gln | | | 360 | | | | | 365 | | | |
| 45 | | 370 | | | Glu | | 375 | | | | | 380 | | | | |
| | 385 | | | | Val | 390 | | | | | 395 | | | | | 400 |
| 50 | | | | | 405 Thr | | | | | 410 | | | | | 415 | |
| | | | | 420 | Pro | | | | 425 | | | | | 430 | | |
| | | | 435 | | Cys | | | 440 | | | | | 445 | | | |
| 55 | | 450 | | | Ser | | 455 | | | | | 460 | | | | |
| | | | | | | | | | | - | _ | | | | _ | |

| | | | | | | | | | | 122 | | | - | | | | |
|-----|------------------------|-------------|------------|--------------|-------------------------|--------------|------------|--------------|------------|------------|------------|------------|----------------|----------------|------------|------------|-----|
| | 465 | 5 | | | | 470 | | | | | | | | | | | |
| • | Ile | Phe | Tyr | Lvs | Asn | Δen | C1. | | | _ | 475 | i | | | | 480 | |
| | Phe | Glu | G) v | . yaz | 485 | , veh | | / Asn | Tyr | Lys 490 | Thr | Arg | Ala | Glu | Val 495 | 480 Lys | |
| . 5 | Dha | . . | - G1y | 500 | inr | Leu | Val | . Asn | Arg 505 | Ile | Glu | Leu | Lys | Gly | Ile | Asp | |
| | Pne | гÀЗ | G1u 515 | Asp | Gly | Asn | Ile | Leu 520 | Gly | His | Lys | Met | Glu | 510 Tyr | Asn | Tyr | |
| | Asn | Ser 530 | His | Asn | Val | Tyr | Ile 535 | Met | Ala | Asp | Lys | Pro | Lys | Asn | Gly | Ile | |
| 10 | Lys 545 | Val | Asn | Phe | Lys | Ile 550 | Arg | His | Asn | Ile | Lys | 540 Asp | Gly | Ser | Val | Gln | |
| | Leu | Ala | qaA | His | Tyr | Gln | Gln | Asn | Thr | Pro | 555 Ile | Gly | Asp | Gly | Pro | 560 Val | |
| 15 | Leu | Leu | Pro | Asp | 565 Asn | His | Tyr | Leu | Ser | 570 Thr | Gln | Ser | Ala | Leu | 575 Ser | Lva | |
| .0 | Asp | Pro | Asn | 580 Glu | Lys | Arg | Asp | His | 585 Met | Ile | Leu | Len | Glu | 590 Phe | 261 | -v | |
| | Ala | Ala | 595 Gly | Ile | Thr | His | Gly | 600 Met | Asp | Glu | Lou | The table | 605 | Pne Pro | vaı | Thr | |
| 20 | | 610 | | | | | 615 | | пор | GIU | ьeu | 620 | rys | Pro | Gln | Glu | |
| | | | (2) | INF | ORMA | TION | FOR | SEQ | ID | NO:5 | 8: | | | | | | |
| 25 | | | (A) | PENG, | TH: | 1815 | bas | ISTI e pa | CS: irs | | | | | | | | |
| 20 | | | (C) s | STRAI | : nuc NDEDI LOGY: | VESS: | si | nale | | | | | | | | | |
| 30 | | (ii | | LEC | JLE 1 | | | | | | | | | | | | |
| | | , | | | | | | | | | | | | | | | |
| | | | (B) | LOCA | TION R IN | : 1. | 18 | Seq | ueno | e | | | | | | | |
| 35 | | (xi | | | | | | ON: | SEO | TD M | 0.50 | | | | | | |
| | ATG G | CG G | CG G | CG G | CG G | CG (2) | CG G | | aa ~ | | | | | | | | |
| 40 | Met A | la A | la A | la A | la A | la A | la G | ly P | ro G 1 | IU M | et V | TC Co | GC G(rg G) | GG CA Ly GI | ln V | TG al | 48 |
| | TTC G | AC GI | rg go | GG C | CG CC | GC TA | AC A | CT A | AT C | TC TO | CG TA | AC AT | rc go | | | 3C | 96 |
| 45 | Phe A | Sp ve | 20 |) Ly Pi | ro Ai | rg Ty | rT | hr A: 25 | 211 TH | eu Se | er Ty | yr I] | le G] 30 | y Gl | u G | ly | 96 |
| | GCC TA | AC GG | C AI | G G1 | T TO | T TC | T G | CT TA | AT G | AT AZ | ייי ריז | רר אז | | | - | _ | |
| | Ala Ty | /r Gl 35 | y Me | t Va | al Cy | 's Se | r A] | La ly | r As | p As | n Le | u As | n Ly | s Va | l Ar | g g | 144 |
| 50 | GTT GC | T AT | C AA | G AA | A AT | C AG | T CC | T TI | T GA | G CA | .C CA | G AC | C TA | C TG | יי רי | c | 100 |
| | 50 | | - | , | | 55 | L FI | .O PII | e G1 | u Hi | s G1 60 | n Th | г ту | r Cy | s Gl | n | 192 |
| 55 | AGA AC Arg Th 65 | C CT | G AG | A GA g Gl | G AT | A AA | A AT | CCT | A CT | G CG | C TT | C AG | A CA | T GAG | S AA | С | 240 |
| | 65 | | | _ ~ | 70 | - - y | - 11 | e ne | ч ге | u Ar | g Ph | e Ar | g Hi | s Glı | As: | n | |
| | | | | | | | | | | | | | | | | | 122 |

| | | | | | | | | | | | | | | GAG Glu | | | 288 |
|----|------------|-----|-----|-----|------------|------------|-----|-----|-----|------------|------------|-----|-----|-------------------|------------|------------|-----|
| 5 | | | | | | | | | | | | | | CTT Leu | | | 336 |
| 40 | | | | 100 | | | | _ | 105 | | | | - | 110 | | - | |
| 10 | | | | | | | | | | | | | | TAT Tyr | | | 384 |
| 15 | | | | | | | | | | | | | | AAT Asn | | | 432 |
| 20 | His | | | | | Pro | | | | | Leu | | | ACT Thr | | Asp | 480 |
| 20 | 145 CTC | AAG | ATC | TGT | GAC | 150 TTT | GGC | CTT | GCC | CGT | 155 GTT | GCA | GAT | CCA | GAC | 160 CAT | 528 |
| 25 | Leu | Lys | Ile | Cys | Asp 165 | Phe | Gly | Leu | Ala | Arg 170 | Val | Ala | Asp | Pro | Asp 175 | His | |
| 25 | | | | | | | | | | | | | | TGG Trp 190 | | | 576 |
| 30 | | | | | | | | | | | | | | TCC Ser | | | 624 |
| 35 | | | | | | | | | | | | | | AAC Asn | | | 672 |
| 40 | _ | | | | | | | | | | | | | ATC Ile | | | 720 |
| | _ | | | | | | | | | | | | | ATA Ile | | | 768 |
| 45 | | | | | | | | | | | | | | AAG Lys 270 | | | 816 |
| 50 | | | | | | | | | | | | | | GAT Asp | | | 864 |
| 55 | | | | | | | | | | | | | | GTT Val | | | 912 |

| | GCT CTG GCC CAC CCG TAC CTG GAG CAG TAT TAT GAC CCA AGT GAT GAG 960 |
|----|--|
| 5 | 305 310 315 Ser Asp Glu 320 |
| | CCC ATT GCT GAA GCA CCA TTC AAG TTT GAC ATG GAG CTG GAC GAC TTA 1008 Pro Ile Ala Glu Ala Pro Phe Lys Phe Asp Met Glu Leu Asp Asp Leu 325 330 335 |
| 10 | CCT AAG GAG AAG CTC AAA GAA CTC ATT TTT GAA GAG ACT GCT CGA TTC 1056 Pro Lys Glu Lys Leu Lys Glu Leu Ile Phe Glu Glu Thr Ala Arg Phe 340 345 350 |
| 15 | CAG CCA GGA TAC AGA TCT ATG GAT CCA CCG GTC GCC ACC ATG GTG AGC 1104 Gln Pro Gly Tyr Arg Ser Met Asp Pro Pro Val Ala Thr Met Val Ser 355 360 365 |
| 20 | AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu 370 370 380 |
| 25 | GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu 395 400 |
| | GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC 1248 Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr 405 410 415 |
| 30 | GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr 420 425 430 |
| 35 | GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp 435 440 445 |
| 40 | TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile 450 450 450 |
| 45 | TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG AAG TTC Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe 470 480 |
| | GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe 485 490 495 |
| 50 | AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn 500 505 510 |
| 55 | AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys 515 520 525 |
| | |

| 5 | | AAC Asn 530 | | | | | | | | | | | | | | | 1632 |
|----|------------|-------------------|-------------------|----------------------|---------------------|-------------------------------|-----------------------|---------------------|------------|-----------|------------|------------|------------|------------|-----------|------------|------|
| | | GAC Asp | | | | | | | | Ile | | | | | | | 1680 |
| 10 | | CCC Pro | | | | | | | | | | | | | | | 1728 |
| 15 | | AAC Asn | | | | | | | | | | | | | | | 1776 |
| 20 | | GGG Gly | | | | | | | | | | | STAA | | | | 1815 |
| | | | (2) | INI | ORM | OITA | ı FOF | R SEQ | O ID | NO: | 59: | | | | | | |
| 25 | | (i | (A) (B) (C) | LENC TYPE STRA | TH: : an MDEI | CHARA 604 nino ONESS | amir acio S: si | no ad l ingle | cids | | | | | | | | |
| 30 | | | Li) N | OLEC | ULE | TYPE | E: p1 | rotei | | | | | | | | | |
| 35 | | () | ci) S | EQUE | NCE | DESC | CRIPT | CION | : SEÇ |) ID | NO:5 | 9: | | | | | |
| | 1 | Ala Asp | | | 5 | | | - | | 10 | | | _ | - | 15 | | |
| 40 | Ala | Tyr | - | 20 Met | Val | Cys | Ser | | 25 Tyr | Asp | Asn | Leu | | 30 Lys | Val | Arg | |
| | Val | Ala 50 | 35 Ile | Lys | Lys | Ile | Ser 55 | 40 Pro | Phe | Glu | His | Gln 60 | 45 Thr | Tyr | Cys | Gln | |
| 45 | Arg 65 | Thr | Leu | Arg | Glu | Ile 70 | Lys | Ile | Leu | Leu | - | Phe | _ | | Glu | Asn 80 | |
| | Ile | Ile | Gly | Ile | Asn 85 | Asp | Ile | Ile | Arg | Ala 90 | Pro | Thr | Ile | Glu | Gln 95 | Met | |
| | Lys | Asp | Val | Tyr 100 | Ile | Val | Gln | Asp | Leu 105 | Met | Glu | Thr | Asp | Leu 110 | Tyr | Lys | |
| 50 | Leu | Leu | Lys 115 | Thr | Gln | His | Leu | Ser 120 | Asn | Asp | His | Ile | Cys 125 | Tyr | Phe | Leu | |
| | Tyr | Gln 130 | Ile | Leu | Arg | Gly | Leu 135 | Lys | Tyr | Ile | His | Ser 140 | Ala | Asn | Val | Leu | |
| | | Arg | Asp | Leu | Lys | | Ser | Asn | Leu | Leu | | Asn | Thr | Thr | Cys | _ | |
| 55 | 145 Leu | Lys | Tle | Cve | Asn | 150 Phe | Glv | Len | A1- | A ~~ | 155 Val | Δls | Δεν | Dro | λεν | 160 His | |
| | | / | | J, 5 | | | ~ _ Y | u | ALA | ~- y | AGT | 710 | o P | | പാവ | **** | |

| | | | | | | | | 126 | | | | | | |
|----|---------------------------|-----------------------|--------------|--------------|-------------|------------|------------|---------------|-------------------|--------------|-------|-----------|------|------------|
| | Asp H | lic Thr | 21 71 | 55 | | | | 170 | | | | | 175 | ; |
| | | lis Thr | | | | | | | | | | | | |
| 5 | | ro Glu 195 | | | | | | | | | Lys | Ser | | |
| | | rp Ser 10 | | | | Leu | | | | Leu | | | | |
| | Ile P. 225 | he Pro | Gly Ly | s His | Tyr | Leu | Asp | Gln | Leu | 220 Asn 1 | lis : | Ile | Leu | Gly |
| 10 | Ile L | eu Gly | Ser Pr | o Ser | Gln | Glu | Asp | Leu | 235 Asn (| Cys 1 | le : | [le | Asn | 240 Leu |
| | | la Arg | Asn Ty | | | | | | | | | | | |
| 45 | | sn Arg | | | | | | | | | | | | |
| 15 | | 275 /s Met] 90 | | | | | | | | | | | | |
| | | 00 eu Ala I | | | | | | | | | | | | |
| 20 | | | | | | | | | | | | | | |
| | | e Ala (| | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| 25 | | o Gly T | | | | | | | | | | | | |
| | | y Glu G O | | | | | | | | | | | | |
| | 385 | y Asp V | al Asn | Gly : | His 1 | Lys I | Phe S | Ser V | al S | er G | y G | lu G | ly (| Glu |
| 30 | | Ala T | hr Tyr | | | | | | | | | | | |
| | Gly Lys | | | | | | | | | | | | | |
| 35 | Gly Val | | | | | | | | | | | | | |
| 55 | Phe Phe | | | | | | | | | | | | | |
| | Phe Phe | Lys As | p Asp | Gly A | 55 Sn T | yr L | ys T | hr A | 46 | 0 a G1 | u 112 |) 1, | ·- r | |
| 40 | Glu Gly | Asp Th | r Leu | 470 Val A | sn A | rq I | le G | 4' 111 T.4 | 75 =11 T.v | c Cl | . Tl | - n | 4 | 80 |
| | Lys Glu | Asp Gl | 485 y Asn | Ile L | eu G | - lv н | 4: is L | 90 Vg. T.4 | ou 2) | | y 11 | 4 9 | 5 P | ne |
| | Ser His | 50 Asn Va | 0 l Tyr | Ile M | et A | 5. | 05 8n L | , c _ C1 | -u G ₁ | и ту. | 51 | n 1y 0 | T A | sn |
| 45 | Val Asn 530 | 515 Phe Ly | s Ile | Ara H | 52 | 20 20 | | , s G | | 525 | 1 G1; | y II | еL | ys |
| | 530 Ala Asp | His Tv | r Gln | 5. 31 n A | 35 | 311 I. | .e G | LU AS | 54 (| y Sei D | · Va | l Gl | n L | eu |
| 50 | Ala Asp 545 Leu Pro | | | | | | | | | | | | | |
| | Leu Pro | Glu Ise | 565 | т.Хт. Г(| ⊭u Se | er Th | r Gl 57 | n Se '0 | r Ala | i Leu | Ser | Г Ly: | s As | σp |
| | Pro Asn | 580 Tle mb | Arg A | asp Hi | ıs Me | t Va 58 | l Le 5 | u Le | u Glı | Phe | Val | Th: | r Al | la |
| 55 | Ala Gly | 595 | . тел (| aly Me | et As 60 | p Gl | u Le | и Ту | r Lys | 1 | | | | |

| | | | | | | | | | | 121 | | | | | | |
|----|-----|-------------------|-------------------|----------------------|--|-----------------------|----------------|-----------------------|-------|------|-----|-----|--|-----|--------------|-----|
| | | | (2 | INI | FORM | ATIO | 1 FOI | R SE | Q ID | NO: | 50: | | | | | |
| 5 | | (: | (A) (B) (C) | LENG TYPI STRA | NCE (GTH: E: nu ANDEI OLOG! | 251: ucle: ONES | l bas ic ac | se pa cid ingle | airs | | | | | | | |
| 10 | | | ix) | FEAT | | | | | | | | • | | | | |
| 15 | | | (B) | LO | ME/KI CATIO HER : | ON: 3 | 1 | 2508 | equer | ice | | | | | | |
| | | (; | xi) s | EQUI | ENCE | DESC | CRIP | rion | : SE(| Q ID | NO: | 60: | | | | |
| 20 | | GAG Glu | | | | | | | | | | | | | | 48 |
| | | GGG Gly | | | | | | | | | | | | | GAA Glu , | 96 |
| 25 | | CTG Leu | | | | | | | | | | | | | | 144 |
| 30 | | GAC Asp 50 | | | | | | | | | | | | | | 192 |
| 35 | | CTT Leu | | | | | | | | | | | | | | 240 |
| 40 | | CAG Gln | | | | | | | | | | | | | | 288 |
| 45 | | CTG Leu | | | | | | | | | | | | | | 336 |
| 70 | | TCC Ser | | | | | | | | | | | | | | 384 |
| 50 | | GAG Glu 130 | | | | | | | | | | | | | | 432 |
| 55 | Cys | GCA Ala | Gln | Ser | | His | Glu | Tyr | | Arg | Gly | Glu | | His | | 480 |

| | The one or | | | |
|----|---|---|---|------|
| 5 | TAT CTG GAC AGC ATG T Tyr Leu Asp Ser Met I 165 | ITT TTT GAC CGC Phe Phe Asp Arg | TTT CTC CAG TGG AAG TGG TTG Phe Leu Gln Trp Lys Trp Leu | 528 |
| 3 | GAA AGG CAA CCG GTG A Glu Arg Gln Pro Val I 180 | ACC AAA AAC ACT Thr Lys Asn Thr 185 | TTC AGG CAG TAT CGA GTG CTA Phe Arg Gln Tyr Arg Val Leu 190 | 576 |
| 10 | GGA AAA GGG GGC TTC G Gly Lys Gly Gly Phe G 195 | GGG GAG GTC TGT ly Glu Val Cys 200 | GCC TGC CAG GTT CGG GCC ACG Ala Cys Gln Val Arg Ala Thr 205 | 624 |
| 15 | 210 | 215 | GAG AAG AAG AGG ATC AAA AAG Glu Lys Lys Arg Ile Lys Lys 220 | 672 |
| 20 | 225 23 | 30 | GAG AAG CAG ATC CTC GAG AAG Glu Lys Gln Ile Leu Glu Lys 235 240 | 720 |
| 25 | 245 | tar Ash Leu | GCC TAT GCC TAC GAG ACC AAG Ala Tyr Ala Tyr Glu Thr Lys 250 255 | 768 |
| 20 | 260 | 265 | ATG AAT GGG GGT GAC CTG AAG Met Asn Gly Gly Asp Leu Lys 270 | 816 |
| 30 | 275 | 280 | GGC TTC GAG GAG GAG CGG GCC Gly Phe Glu Glu Glu Arg Ala 285 | 864 |
| 35 | 290 | 295 | GGC TTA GAA GAC CTC CAC CGT Gly Leu Glu Asp Leu His Arg 300 | 912 |
| 40 | 305 310 |) | CT GAA AAC ATC CTG TTA GAT TO Glu Asn Ile Leu Leu Asp 315 320 | 960 |
| 45 | 325 | 3: | TG GGC TTG GCT GTG AAG ATC eu Gly Leu Ala Val Lys Ile 30 335 | 1008 |
| | 340 | 345 | TG GGC ACT GTT GGC TAC ATG al Gly Thr Val Gly Tyr Met 350 | 1056 |
| 50 | 355 | 360 | r Gly Leu Ser Pro Asp Tyr 365 | 1104 |
| 55 | TGG GGC CTT GGC TGC CTC Trp Gly Leu Gly Cys Leu 370 | ATC TAT GAG AT Ile Tyr Glu Me 375 | TG ATC GAG GGC CAG TCG CCG et Ile Glu Gly Gln Ser Pro 380 | 1152 |
| | | | | 400 |

| 5 | | | _ | | AAG Lys | _ | | _ | | | | | 1200 |
|----|---|---|---|---|-------------------|---|---|---|--|--|--|---|------|
| · | | | | | GAG Glu 405 | | | | | | | | 1248 |
| 10 | | | | | AAG Lys | | | | | | | | 1296 |
| 15 | | | | | GAG Glu | | | | | | | | 1344 |
| 20 | | | | | TTC Phe | | | | | | | | 1392 |
| 25 | | _ | | | ccc Pro | | _ | | | | | | 1440 |
| | | _ | | | ACT Thr 485 | | | | | | | | 1488 |
| 30 | | | | | AAG Lys | | | | | | | | 1536 |
| 35 | | | | | GAA Glu | | | | | | | _ | 1584 |
| 40 | | | _ | | CTC Leu | | | | | | | | 1632 |
| 45 | | | | | GGG Gly | | | | | | | | 1680 |
| | | | | | AGT Ser 565 | | | | | | | | 1728 |
| 50 | _ | | | | CAT His | | | | | | | | 1776 |
| 55 | | | | _ | ACC Thr | | | | | | | | 1824 |

| 5 | 610 | | 615 | neu Asp | GIY ASP Val 620 | AAC GGC CAC AAG Asn Gly His Lys | 1872 |
|----|-----------------------------------|-----------------------------------|-------------------------------|-----------------------------|-------------------------------------|---|------|
| | TTC AGC GT Phe Ser Va 625 | 7 | GAG GGC (Glu Gly (630 | GAG GGC (Glu Gly 1 | GAT GCC ACC Asp Ala Thr 635 | TAC GGC AAG CTG Tyr Gly Lys Leu 640 | 1920 |
| 10 | ACC CTG AA Thr Leu Ly | G TTC ATC s Phe Ile 645 | TGC ACC A Cys Thr T | mr Gry I | AAG CTG CCC Lys Leu Pro | GTG CCC TGG CCC Val Pro Trp Pro 655 | 1968 |
| 15 | ACC CTC GT Thr Leu Va | G ACC ACC (1 Thr Thr 1 660 | CTG ACC T Leu Thr T | AC GGC G yr Gly V 665 | GTG CAG TGC : Val Gln Cys 1 | TTC AGC CGC TAC Phe Ser Arg Tyr 670 | 2016 |
| 20 | CCC GAC CAG Pro Asp His 675 | C ATG AAG (s Met Lys (| AH HIS A | AC TTC T sp Phe P 80 | ne Lys Ser A | GCC ATG CCC GAA lla Met Pro Glu 85 | 2064 |
| 25 | GGC TAC GTO Gly Tyr Val 690 | C CAG GAG C L Gln Glu A | GC ACC AT rg Thr II 695 | TC TTC T le Phe Pl | TC AAG GAC G he Lys Asp A 700 | AC GGC AAC TAC sp Gly Asn Tyr | 2112 |
| | 705 | 7 | 10 | ie Giu G | 1y Asp Thr L 715 | TG GTG AAC CGC eu Val Asn Arg 720 | 2160 |
| 30 | | 725 | re wah M | е Lys G1 73 | u Asp Gly A | AC ATC CTG GGG sn Ile Leu Gly 735 | 2208 |
| 35 | | 740 | ··· IYI AS | 745 | s Asn Val Ty | AT ATC ATG GCC r Ile Met Ala 750 | 2256 |
| 40 | GAC AAG CAG Asp Lys Gln 755 | AAG AAC GG Lys Asn Gl | C ATC AAG y Ile Lys 760 | VAL AS | C TTC AAG AT n Phe Lys Il 76 | C CGC CAC AAC e Arg His Asn 5 | 2304 |
| 45 | 770 | | 775 | ı Ala Ası | p His Tyr Gl 780 | G CAG AAC ACC n Gln Asn Thr | 2352 |
| | CCC ATC GGC Pro Ile Gly 785 | GAC GGC CC Asp Gly Pro | o var neu | CTG CCC | GAC AAC CA Asp Asn Hi | C TAC CTG AGC S Tyr Leu Ser 800 | 2400 |
| 50 | ACC CAG TCC Thr Gln Ser | GCC CTG AGG Ala Leu Sei 805 | C AAA GAC | CCC AAC Pro Asn 810 | l Glu Lys Arg | C GAT CAC ATG Asp His Met 815 | 2448 |
| 55 | GTC CTG CTG (Val Leu Leu (| GAG TTC GTO Glu Phe Val 320 | ACC GCC Thr Ala | GCC GGG Ala Gly 825 | ATC ACT CTC | GGC ATG GAC Gly Met Asp 830 | 2496 |

131

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GAG CTG TAC AAG TAA
                                                                   2511
     Glu Leu Tyr Lys
            835
5
             (2) INFORMATION FOR SEQ ID NO:61:
           (i) SEQUENCE CHARACTERISTICS:
10
            (A) LENGTH: 836 amino acids
             (B) TYPE: amino acid
            (C) STRANDEDNESS: single
             (D) TOPOLOGY: linear
15
           (ii) MOLECULE TYPE: protein
           (v) FRAGMENT TYPE: internal
           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:
20
     Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg
                  5
                           10
     Glu Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu
                20
                                 25
     Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr
25
                              40
     Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg
                          55
     Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr
                                         75
             70
30
     Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu
                                     90
     Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro
                100
                       105 110
     Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln
35
                              120
                                                125
     Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala
         130 135
                                            140
     Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu
                      150
                                         155 160
40
     Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu
                  165
                                    170
     Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu
                                  185
                180
     Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr
45
           195
                              200
                                                205
     Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys
                 215 220
     Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys
                       230
50
     Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys
                           250
                  245
     Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys
                                  265
     Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala
55
                               280
     Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg
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| 290 295 300 Glu Asn Thr Val Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp 305 Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile 307 Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile 330 Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile 340 Fro Glu Gly Asp Leu Ile Arg Gly Arg Val Gly Thr Val Gly Tyr Met 345 Ala Pro Glu Val Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr 355 Ala Pro Gly Leu Gly Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro 370 370 Phe Arg Gly Arg Lys Glu Lys Val Lys Arg Glu Gly Val Asp Arg Arg 385 390 Val Leu Glu Thr Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala 405 Lys Ser Ile Cys Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu 400 Gly Cys Gln Glu Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe 445 Asp Asp Arg Asn Met Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro 455 Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Pro Pro 465 Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile 465 Asp Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln 500 Asn Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly 515 Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Glu 515 Asp Pro Pro Lys Lys Gly Leu Gln Arg Leu Glu Arg Leu Asp His Thr Asp Asp 490 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 550 Fo Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Asn His Pro 560 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 555 Fro Pro Val Ala Thr Met Val Glu Leu Asp Gly Asn His Cys Glo Phe Ser Asn His Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp 555 Fo Pro Val Ala Thr Met Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Glo Phe Ser Val Ser Gly Glu Glu Gly Asp Ala Thr Tyr Gly Lys Leu 660 Asp Asp Asp His Wal Thr Leu Thr Tyr Gly Val Glu Cys Phe Ser Arg Tyr 660 Asp Asp His Met Lys Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu 660 Asp Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 665 Asp Cys Thr Leu Lys Phe Ile Cys Thr Thr | | | | | | | | | | | | 132 | ? | | | | | | |
|--|----|------------|------|------------|------------|------------|------------|-------|------|------------|------|----------|-------------|-------------|------------|----------|------------|------------|------------|
| Sind Ash Thr Val Tyr Arg Asp Leu Lys Pro Glu Ash Ile Leu Leu Asp 305 310 320 325 325 326 325 335 335 335 335 335 345 335 335 345 335 335 345 336 345 336 365 366 365 366 366 366 367 370 375 370 375 376 | | | | | | | | 2 | 95 | | | | | 3 | 0.0 | | | | |
| Asp Tyr Gly His Ile Arg Ile Ser Asp Leu Gly Leu Ala Val Lys Ile 325 326 327 336 336 346 346 346 347 348 348 348 349 348 349 341 349 341 340 342 341 345 360 365 366 365 367 367 370 375 376 376 376 377 375 376 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 375 376 377 377 375 376 377 375 376 377 377 375 376 377 377 377 377 377 377 377 377 377 | | | | | | | | | | | | | | lu A | sn I | | | | |
| Pro Glu Gly Asp Leu Ile Arg Gly Arg Val Gly Try Net 360 | 5 | Asp | э Ту | r Gl | у Н | is I 3 | le A 25 | rg I | le | Ser | Ası | Le | u G] | гэ Гу Ье | eu A | la ' | Val | | |
| Ala Pro Glu Val Leu Asn Asn Gln Arg Tyr Gly Leu Ser Pro Asp Tyr 350 360 365 360 365 360 365 360 365 360 365 360 370 370 385 380 380 380 380 380 380 38 | | Pro | Gl | u Gl | у Аз 34 | sp L | eu I | le A | rg | Gly | Arg | y Va | 1 G1 | ут | ır V | al (| Gly | Ту | r Met |
| 10 Trp Gly Leu Gly Cys Leu Ile Tyr Glu Met Ile Glu Gly Gln Ser Pro 370 370 380 Phe Arg Gly Arg Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg 385 390 395 400 Val Leu Glu Thr Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala 405 410 415 Lys Ser Ile Cys Lys Met Leu Leu Thr Lys Asp Ala Lys Gln Arg Leu 420 425 430 445 Oliv Cys Gln Glu Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe 450 445 Arg Asn Met Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro 450 455 Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Pro Pro 465 485 Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln 500 Asn Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly 515 Asn Asn Ser Lys Gly Leu Leu Gln Arg Leu Asn Arg Asn His Pro Pro Glu 545 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 545 11e Asn Ser Asn His Val Ser Leu Asp Gly Asp Val Asn Gly His Lys 610 Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Ala Thr Tyr Gly Lys Leu 620 Arg Asn His Val Gly Glu Gly Asp Ala 630 Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 630 Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 650 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 650 Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys 660 Asn Asn Ser Val Ser Gly Glu Gly Glu Glu Leu Phe Thr Gly 660 For Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 660 Asn Asn Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu 661 Find Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 660 Gly Tyr Val Gln Glu Arg Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 660 Gly Tyr Val Gln Glu Arg Thr Thr File Phe Phe Lys Asp Asp Gly Asn Tyr 660 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Ser Ala Met Pro Glu 675 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Ser Ala Met Pro Glu 675 Glu Leu Lys Gly Ile Asp Phe Lys Gly Glu Asp Gly Asn Tle Leu Cly 550 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 710 710 710 Tile Glu Leu Lys Gly Ile Asp Phe Lys Gly Asp Gly Asn Tle Leu | | Ala | Pr | o Gl 35 | u Va | il L | eu A | sn A | sn | Gln | Arg | , ГТу | r Gl | у Ье | eu S | er 1 | 350 Pro | Asp | Tyr |
| Phe Arg Gly Arg Lys Glu Lys Val Lys Arg Glu Glu Val Asp Arg Arg 385 | 10 | | | | | | | eu I | le ' | | | | | | | | | | |
| Val Leu Glu Thr Glu Glu Val Tyr Ser His Lys Phe Ser Glu Glu Ala 405 | | | | | | | /s G | lu L | | | | | | | | | | | |
| Lys Ser Ile Cys Lys Met Leu Leu Thr Lys Asp Ala Lys Gin Arg Leu 420 425 430 430 435 430 Gil Glu Glu Glu Glu Glu Glu Glu Glu Glu Gl | | | | | | | | | | | | | | | | | | | |
| Gly Cys Gln Glu Glu Gly Ala Ala Glu Val Lys Arg His Pro Phe Phe Ass Net Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro Asp Ass Net Asn Phe Lys Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Pro Pro Asp Ass Net Asn Phe Lys Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Afs Ass Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Afs Ass Leu Asp His Thr Asp Asp Asp Ass Asp Pro Pro Asp Ass Ass Leu Asp His Thr Asp Asp Ass Ass Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Pro Glu Sin Sin Ass Gly Thr Leu Pro Pro Asp Leu Asn Arg Ass His Pro Pro Glu Sin Ass Gly Thr Leu Pro Pro Asp Leu Asn Arg Ass His Pro Pro Glu Sin Ass Ass Ass Ass Ass Ass Ass Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Pre Ass His Ris Gln Sin Ass Ass Ass Ass Ass Ass Ass Ass Ass As | 15 | | | | | | | | | | | | | | | | | | |
| 20 Arg Asn Met Asn Phe Lys Arg Leu Glu Ala Gly Met Leu Asp Pro Pro Asp Phe Val Pro Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Asp Pro Arg Ala Val Tyr Cys Lys Asp Val Leu Asp Ile Asp | | | | | | | | | | | | | | | | | | | |
| # A50 | 20 | | | | | | | | | | | | | | | | | | |
| Single S | 20 | | | | | | | | | | | | | | t Le | u A | | | |
| Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln | | | | | | | | | | | | | | | | | | | |
| Asp Phe Tyr Ser Lys Phe Ser Thr Gly Ser Val Ser Ile Pro Trp Gln | 25 | Glu | GIn | Phe | Sei | Th 48 | r Va 5 | l Ly | s G | ly ' | Val | Asn | Leu | as, | Hi. | s Tl | hr i | Asp | Asp |
| Asn Glu Met Ile Glu Thr Glu Cys Phe Lys Glu Leu Asn Val Phe Gly 515 30 Pro Asn Gly Thr Leu Pro Pro Asp Leu Asn Arg Asn His Pro Pro Glu 530 Pro Pro Lys Lys Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln 545 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 565 Ile Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp 580 Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 595 40 Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys 610 Phe Ser Val Ser Gly Glu Glu Gly Asp Ala Thr Tyr Gly Lys Leu 625 Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 645 Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr 660 Pro Asp His Met Lys Gln His Asp Phe Phe Lys Asp Asp Gly Asn Tyr 660 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 660 Gly Tyr Val Gln Glu Val Lys Phe Glu Gly Asp Gly Asp Ile Leu Val Asn Arg 705 Tle Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 10 Thr Leu Glu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 11 Asn Arg 705 Table Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 12 Thr Leu Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 13 Table Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 14 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 15 Table Clu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 16 Table Clu | | Asp | Phe | Tyr | Ser 500 | Ly | s Ph | e Se | r T | hr (| Gly | Ser | Val | Sei | : Il | e Pi | 20 : | 195 Trp | Gln |
| Pro | | Asn | Glu | Met 515 | Ile | Glı | ı Th | r Gl | u C | ys 1 | Phe | Lys | Glu | Leu | As: | n Va | LO al I | he | Gly |
| Pro Pro Lys Lys Gly Leu Leu Gln Arg Leu Phe Lys Arg Gln His Gln 545 Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 565 Ile Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp 590 Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 595 40 Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys 615 Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu 625 Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 660 Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 695 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Gly Asp Ile Leu Val Asn Arg 705 Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly Gly Ile Gly Ile Gly Ile Asp Phe Lys Glu Asp Ile Leu Gly Gly Ile Gly Ile Asp Phe Lys Glu Asp Ile Leu Gly | 30 | | | | | | | o Pro |) A | | | | | Asn | 52: Hi: | | | | |
| Asn Asn Ser Lys Ser Ser Pro Ser Ser Lys Thr Ser Phe Asn His His 575 11e Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp 580 580 585 585 585 580 580 585 585 580 580 585 585 580 580 580 585 585 580 580 580 585 580 580 580 580 585 580 | | Pro 545 | Pro | Lys | Lys | Gly | / Let | ı Leı | 1 G) | ln A | ırg | Leu | Phe | 540 Lys | Arg | g Gl | n H | lis | Gln |
| The Asn Ser Asn His Val Ser Ser Asn Ser Thr Gly Ser Ser Arg Asp 590 | 35 | | | | | Ser | Ser | | | | er : | Lys | | | | | | | |
| Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly 595 | | | | | Asn | | | | | r A | sn : | | | | | | | | |
| 40 Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys 610 615 620 Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu 625 630 635 640 Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 645 655 Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr 660 665 665 665 Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 675 680 685 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 695 700 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 710 715 720 Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | | Pro 1 | Pro | Val 595 | Ala | Thr | Met | Val | Se | r L | ys (| Gly | Glu | Glu | Leu | 59 Ph | 0 e T | hr (| Gly |
| Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu 625 | 40 | | | | | | | Glu | Le | | | | | Val | | | | | |
| Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro 645 Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr 660 Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 675 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | | Phe 5 | Ser | Val | Ser | Gly | Glu | Gly | Gl | u G | ly A | Asp A | Ala | 620 Thr | Tyr | Gl | y L | ys 1 | Leu |
| Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr 660 Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 675 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | 45 | Thr I | eu . | Lys | Phe | Ile | Cys | Thr | Th | r G | ly I | ys) | 635 Leu | Pro | Val | Pro | T | rp I | 540 Pro |
| Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu 675 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 Tle Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | | | | | | | | | | r G | ly V | | | | | | | | |
| Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 690 695 700 Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 710 725 Tle Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | | | | | | | | | Ası | Pl (Q c | | | | | | | | | |
| Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 705 710 715 720 Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | 50 | | | | | | | Thr | | | | | | | | | | | |
| Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly | | | | | | | Val | | | | | | | | | | | | |
| | 55 | Ile G | lu I | Leu I | Lys (| Gly 725 | Ile | Asp | Phe | . Ly | s G | lu A | 15 .sp (| Gly . | Asn | Ile | Le | 7 u G | 20 ly |
| His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala | | | | | | | | | | | | | | | | | | | |

| | | | | 740 | | | | | 745 | | | | | 750 | | | | |
|---------|---|------------|------------|---------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-----|-----|
| | Asp | Lys | Gln 755 | Lys | Asn | Gly | Ile | Lys 760 | Val | Asn | Phe | Lys | Ile 765 | Arg | His | Asn | | |
| 5 | Ile | Glu 770 | Asp | Gly | Ser | Val | Gln 775 | Leu | Ala | Asp | His | Tyr 780 | Gln | Gln | Asn | Thr | | |
| | Pro 785 | | Gly | Asp | Gly | Pro 790 | Val | Leu | Leu | Pro | Asp 795 | Asn | His | Tyr | Leu | Ser 800 | | |
| | Thr | Gln | Ser | Ala | Leu 805 | Ser | Lys | Asp | Pro | Asn 810 | Glu | Lys | Arg | Asp | His 815 | Met | | |
| 10 | Val | Leu | Leu | Glu 820 | Phe | Val | Thr | Ala | Ala 825 | Gly | Ile | Thr | Leu | Gly 830 | Met | Asp | | |
| | Glu | Leu | Tyr 835 | Lys | | | | | | | | | | | | | | |
| 15 | | | (2) | INI | FORM | OITA | I FOR | R SE(| O ID | NO: 6 | 52: | | | | | | | |
| | | (i | | EQUEN | | | | | | | | | | | | | | |
| | (A) LENGTH: 1893 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | | | | | | | | | | | | | | | | | |
| 20 | | | | STRA | | | | ~ | 2 | | | | | | | | | |
| | | | | OLEC FEATU | | TYPI | E: cI | ANC | | | | | | | | | | |
| 25 | (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1 1890 | | | | | | | | | | | | | | | | | |
| | (A) NAME/KEY: Coding Sequence (B) LOCATION: 11890 (D) OTHER INFORMATION: | | | | | | | | | | | | | | | | | |
| | • | | | | | | | | | | | | | | | | | |
| 30 | | () | (i) 5 | EQUE | ENCE | DESC | RIPT | rion | : SE(|) ID | NO: | 52: | | | | | | |
| | | | | AGC Ser | | | | | | | | | | | | | 48 | |
| 25 | 1 | | 5 | | 5 | 5 | | | | 10 | -1- | - | | - | 15 | 2 | | |
| 35 | | | | TTC | | | | | | | | | | | | | 96 | |
| | Asp | Ser | Thr | Phe 20 | Thr | Val | Leu | Lys | Arg 25 | Tyr | Gln | Asn | Leu | J0 | Pro | Ile | | |
| 40 | GGC | TCA | GGA | GCT | CAA | GGA | ATA | GTA | TGC | GCA | GCT | тат | GAT | GCC | TTA | CTT | 144 | |
| | Gly | Ser | Gly 35 | Ala | Gln | Gly | Ile | Val 40 | Cys | Ala | Ala | Tyr | Asp 45 | Ala | Ile | Leu | | |
| | GAA | AGA | ДДТ | GTT | GCA | ATC | DAG | AAG | СТА | AGC | CGA | CCA | ւեւգեւ | CAG | таа | CAG | 192 | |
| 45 | | Arg | | Val | | | Lys | | | | Arg | Pro | | | | | 172 | |
| | | 50 | | | | | 55 | | | | • | 60 | | | | | | |
| | | | | AAG Lys | | | | | | | | | | | | | 240 | |
| 50 | 65 | | | | | 70 | | | | | 75 | | | | | 80 | | |
| | | | | AAT Asn | | | | | | | | | | | | | 288 | |
| <i></i> | TOU | 11.1.0 | Lys | YOU | 85 | 110 | Cly | Leu | neu | 90 | vaı | FIIG | TIIL | 110 | 95 | ניעם | | |
| 55 | TCC | CTA | GAA | GAA | TTT | CAA | GAT | GTT | TAC | ATA | GTC | ATG | GAG | CTC | ATG | GAT | 336 | |
| | | | | | | | | | | | | | | | | | • | 133 |

| | | | | | | | | | | | | 34 | | | | | | | | |
|----|-----------------------|-------------------|--------------------|--------------------|--------------|-------------------|----------------|-------------------|-------------------|-------------------|--------------|----------------|--------------|--------------------|--------------------|-------------------|--------------|----------------|------------|------|
| | | | | | _ | | | | | 10 | 75 | | | | | 11 | LO | | Asp | |
| 5 | GC Al | A A | AT C sn L 1 | TT T eu C 15 | ys (| CAA (Sln) | GTG Val | ATT Ile | CA Gl 12 | II ME | rg g et g | AG lu | CTA Leu | GAT Asp | CA: His | Gl | AA A .u A | .GA .rg | ATG Met | 384 |
| 10 | TC: Se: | C TA | AC C /r L 30 | TT C | TC T eu T | AT C | | ATG Met 135 | CT(Let | з тс и Су | T G | GA ly | ATC Ile | AAG Lys 140 | CAC | CT Le | T C. u H | AT is | TCT Ser | 432 |
| 15 | 145 | 5 | • | FT A | | 1 | 50 | Asp | ъес | т гу | s P | ro | Ser 155 | Asn | Ile | Va. | l Vá | a l | Lys 160 | 480 |
| | | | L -3 | SC AC | 1 | 65 | ys. | 116 | ren | l Asj | p Pi 17 | ne (| Gly | Leu | Ala | Arc | g Th | r 75 | Ala | 528 |
| 20 | • | | | T TT r Ph 18 | 0 | -C PI | - L . | riir. | Pro | 191 185 | c Va | 11 / | /al | Thr | Arg | Тут 190 | ту) | r. | Arg | 576 |
| 25 | GCA Ala | Pro | C GA D Gl 19 | G GT u Va 5 | C A7 | rc ca | TT G | TY | ATG Met 200 | GGC Gly | TA | c z r I | y AAG | GAA Glu | AAC Asn 205 | GTG Val | GA As | T : | TTA Leu | 624 |
| 30 | TGG Trp | Ser 210 | r GT(Va. | G GGG | G ТС У Су | C Al | .C 14 | TG (et (| GGA Gly | GAA Glu | AT Me | G G t V | al (| TGC Cys 220 | CAC His | AAA Lys | AT Il | C (| CTC Leu | 672 |
| 35 | 225 | | 2 | A AGO | , ,,,, | 23 | 0 | 16 1 | Asp | GIN | Tr | 2 2 | sn I 35 | ya , | Val | Ile | Glu | າ G 2 | 1n 40 | 720 |
| | CTT Leu | - | | | 24 | 5 | . | iu r | -ne | met | ьуя 250 | S Ly | ys I | eu (| 3ln | Pro | Thr 255 | · V | al | 768 |
| 40 | AGG . Arg | ACT Thr | TAC | GTT Val 260 | | A AAG | C AC | GA C | 10 | AAA Lys 265 | TAT Tyr | G(| CT G la G | GA T | yr : | AGC Ser 270 | TTT Phe | G. | AG lu | 816 |
| 45 | AAA (| CTC Leu | TTC Phe 275 | CCT Pro | GA1 Asp | GT(| C CI | u P | TC he: 80 | CCA Pro | GCT Ala | GA As | C T | er G | AA (lu H 85 | CAC | AAC Asn | Ai Ly | AA Ys | 864 |
| 50 | CTT A | AAA Lys 290 | GCC Ala | AGT Ser | CAG Gln | GCA Ala | AG Ar 29 | y A | AT ? | rtg Leu | TTA Leu | TC Se | r L | AA A ys M 00 | TG C | TG eu | GTA Val | A7 | ΓA Le | 912 |
| 55 | GAT C Asp A 305 | GCA Ala | TCT Ser | AAA Lys | AGG Arg | ATC Ile 310 | 20 | T G: r Va | TA (| SAT Asp | GAA Glu | GC Al 31 | a Le | rc c eu g | AA C ln H | AC (| CCG Pro | ТА Ту 32 | r | 960 |
| | ATC A | TA | GTC | TGG | TAT | GAT | CC | r TC | CT G | AA (| GCA | GA | A GC | CT CO | CA C | CA (| CCA | AΑ | .G | 1008 |

| | | | | | | | | | | 135 | | | | | | | |
|------|------------|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|------|
| | Ile | Asn | Val | Trp | Tyr 325 | Asp | Pro | Ser | Glu | Ala 330 | Glu | Ala | Pro | Pro | Pro 335 | Lys | |
| 5 | | CCT Pro | | | _ | | | | | | | | | | | | 1056 |
| 10 | | GAA Glu | | | | | | | | | | | | | | | 1104 |
| 15 | | GGA Gly 370 | | | | | | | | | | | | | | | 1152 |
| | | GAT Asp | | | | | | | | | | | | | | | 1200 |
| 20 | | GGG Gly | | | | | | | | | | | | | | | 1248 |
| 25 | | AAG Lys | | | | | | | | | | | | | | | 1296 |
| 30 | | CTG Leu | | | | | | | | | | | | | | | 1344 |
| 35 | | CCC Pro 450 | | | | | | | | | | | | | | | 1392 |
| 33 | | TAC Tyr | | | | | | | | | | | | | | | 1440 |
| 40 | | GAA Glu | | | | | | | | | | | | | | | 1488 |
| 45 | AAC Asn | TAC Tyr | | | CGC Arg | | | | | | | | | | | | 1536 |
| 50 | | CGC Arg | | | | | | | | | | | | | | | 1584 |
| E.E. | | GGG Gly 530 | | | | | | | | | | | | | | | 1632 |
| 55 | ATG | GCC | GAC | AAG | CAG | AAG | AAC | GGC | ATC | AAG | GTG | AAC | TTC | AAG | ATC | CGC | 1680 |

| | 136 | |
|----|--|------|
| | Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg | |
| - | CAC AAC ATC GAG GAC GGC AGC GTG GAG | |
| 5 | 565 570 Fis Tyr Gln Gln 575 | 1728 |
| 10 | AAC ACC CCC ATC GGC GAC GGC CCC GTG CTG CTG CCC GAC AAC CAC TAC Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Pro Asp Asn His Tyr 580 585 590 | 1776 |
| 15 | CTG AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp 595 600 605 | 1824 |
| | CAC ATG GTC CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly 610 620 | 1872 |
| 20 | ATG GAC GAG CTG TAC AAG TAA Met Asp Glu Leu Tyr Lys 625 630 | 1893 |
| 25 | (2) INFORMATION FOR SEQ ID NO:63: | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| 30 | (A) LENGTH: 630 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 35 | (ii) MOLECULE TYPE: protein(v) FRAGMENT TYPE: internal | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:63: | |
| 40 | Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly 1 5 10 15 | |
| | Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile 20 21 22 30 | |
| - | Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asp Val Ala Tla T | |
| 45 | Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln 50 55 60 Thr His Ala Lys Arg Ala Thr Ang Gl | |
| | Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val 65 70 75 80 | |
| 50 | Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys 85 90 Ser Leu Glu Glu Phe Gln Asn Val Thurs | |
| | Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp 100 105 110 Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met 115 120 | |
| Er | Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser | |
| 55 | 130 135 140 Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys | |
| | Let bet Ash the val Val Lys | 120 |

| | | | | | | | | | | 137 | | | | | | |
|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| | Ser | Asp | Cys | Thr | Leu 165 | Lys | Ile | Leu | Asp | Phe 170 | Gly | Leu | Ala | Arg | Thr 175 | Ala |
| 5 | Gly | Thr | Ser | Phe 180 | | Met | Thr | Pro | Tyr 185 | | Val | Thr | Arg | Tyr 190 | | Arg |
| | | | 195 | Val | | | | 200 | _ | | _ | | 205 | | _ | |
| | Trp | Ser 210 | Val | Gly | Сув | Ile | Met 215 | Gly | Glu | Met | Val | Cys 220 | His | Lys | Ile | Leu |
| 10 | Phe 225 | Pro | Gly | Arg | Asp | Tyr 230 | Ile | Asp | Gln | Trp | Asn 235 | Lys | Val | Ile | Glu | Gln 240 |
| | Leu | Gly | Thr | Pro | Cys 245 | Pro | Glu | Phe | Met | Lys 250 | Lys | Leu | Gln | Pro | Thr 255 | Val |
| 15 | Arg | Thr | Tyr | Val 260 | Glu | Asn | Arg | Pro | Lys 265 | Tyr | Ala | Gly | Tyr | Ser 270 | Phe | Glu |
| | Lys | Leu | Phe 275 | Pro | Asp | Val | Leu | Phe 280 | Pro | Ala | Asp | Ser | Glu 285 | His | Asn | Lys |
| | | 290 | | Ser | | | 295 | | | | | 300 | | | | |
| 20 | Asp 305 | Ala | Ser | Lys | Arg | Ile 310 | Ser | Val | Asp | Glu | Ala 315 | Leu | Gln | His | Pro | Tyr 320 |
| | | | | Trp | 325 | _ | | | | 330 | | | | | 335 | - |
| 25 | | | | Lys 340 | | | _ | | 345 | | | | | 350 | | |
| | _ | | 355 | Ile | _ | _ | | 360 | | _ | | | 365 | _ | | - |
| | | 370 | | Ile | | _ | 375 | | | | | 380 | | | | |
| 30 | 385 | | | Pro | | 390 | | | | | 395 | _ | | | | 400 |
| | | | | Val | 405 | | | | | 410 | | | | | 415 | |
| 35 | | _ | | Ser 420 | | | - | | 425 | | - | _ | | 430 | - | _ |
| | - | | 435 | Leu | _ | | | 440 | | | _ | - | 445 | | | |
| 40 | | 450 | | Leu | | | 455 | | | - | - | 460 | | - | | |
| 40 | 465 | | | Asp Tyr | | 470 | _ | | | _ | 475 | | _ | | | 480 |
| | | | | Thr | 485 | | | | | 490 | | | | | 495 | |
| 45 | | | | 500 Glu | | | | | 505 | | | | | 510 | | |
| | | | 515 | Lys | | | | 520 | | | | | 525 | | | |
| -50 | | 530 | | Lys | | | 535 | | | | | 540 | | | | |
| | 545 | | _ | Glu | | 550 | | - | | - | 555 | | | - | | 560 |
| | | | | Ile | 565 | | | | | 570 | | | | | 575 | |
| 55 | | | | 580 | | | | | 585 | | | | | 590 | | Asp |
| | | | | | | | | | | | | | | -,- | 3 | E |

| | 138 | |
|----|---|-----|
| | 595 600 605 | |
| | Als Met val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly | |
| | Met Asp Glu Leu Tyr Lys 620 | |
| 5 | 625 630 | |
| | 050 | |
| | (2) INFORMATION FOR SEQ ID NO:64: | |
| | | |
| 10 | (i) SEQUENCE CHARACTERISTICS: | |
| ,, | (A) LENGTH: 1821 base pairs | |
| | (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| 15 | | |
| 13 | (ii) MOLECULE TYPE: cDNA | |
| | (ix) FEATURE: | |
| | (A) NAME/KEY: Coding Sequence | |
| | (B) LOCATION: 11818 | |
| 20 | (D) OTHER INFORMATION: | |
| ı | (vi) CROWNING - | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64: | |
| | ATG TCT CAG GAG AGG CCC ACG TTC TAC CGG CAG GAG CTG AAC AAG ACA | |
| 25 | Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr | 48 |
| | 1 5 10 15 15 | |
| | | |
| | ATC TGG GAG GTG CCC GAG CGT TAC CAG AAC CTG TCT CCA GTG GGC TCT lle Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser | 96 |
| 30 | | |
| | 30 | |
| | GGC GCC TAT GGC TCT GTG TGT GCT GCT TTT GAC ACA AAA ACG GGG TTA | 144 |
| | 35 Ala Ala Phe Asp Thr Lys Thr Gly Leu | |
| 35 | 40 45 | |
| | CGT GTG GCA GTG AAG AAG CTC TCC AGA CCA TTT CAG TCC ATC ATT CAT | |
| | Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His | 192 |
| | 55 60 | |
| 40 | GCG AAA AGA ACC TAC AGA GAA CTG CGG TTA CTT AAA CAT ATG AAA CAT | |
| | Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Lys His Met Lys His 70 | 240 |
| | 70 75 80 | |
| | | |
| 45 | GAA AAT GTG ATT GGT CTG TTG GAC GTT TTT ACA CCT GCA AGG TCT CTG | 288 |
| | 85 Red Hed Asp val Phe Thr Pro Ala Arg Ser Leu | |
| | 95 | |
| | GAG GAA TTC AAT GAT GTG TAT CTG GTG ACC CAT CTC ATG GGG GCA GAT | 226 |
| 50 | The val Tyr Leu val Thr His Leu Met Gly Ala Age | 336 |
| | 100 105 110 | |
| | CTG AAC AAC ATT GTG AAA TGT CAG AAG CTT ACA GAT GAC CAT GTT CAG | |
| | Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln | 384 |
| 55 | 115 120 125 | |
| 00 | | |
| | TTC CTT ATC TAC CAA ATT CTC CGA GGT CTA AAG TAT ATA CAT TCA GCT | 432 |
| | | 138 |
| | | |

| | | | | | | | | | | 135 | | | | | | | |
|----|-----|------------|-----|-----|-------------------|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------|
| | Phe | Leu 130 | Ile | Tyr | Gln | Ile | Leu 135 | Arg | Gly | Leu | Lys | Tyr 140 | Ile | His | Ser | Ala | |
| 5 | | | | | AGG Arg | | | | | | | | | | | _ | 480 |
| 10 | | | | | AAG Lys 165 | | | | | | | | | | | | 528 |
| | | _ | | | GGC Gly | | | | | | | | | _ | | _ | 576 |
| 15 | | | | | TGG Trp | | | | | | | | | | | | 624 |
| 20 | | | | | ATG Met | | | | | | | | | | | | 672 |
| 25 | | | | | ATT Ile | | | | | | | | | | | | 720 |
| 30 | | | | | GAG Glu 245 | | | | | | | | | | | | 768 |
| 35 | | | | | TCT Ser | | | | | | | | | | | | 816 |
| | | | | | GCC Ala | | | | | | | | | | | | 864 |
| 40 | | | | | TCA Ser | | | | | | | _ | | _ | | _ | 912 |
| 45 | | | | | GCT Ala | | | | | | | | | | | | 960 |
| 50 | | | | | CAG Gln 325 | | | | | | | | | _ | | _ | 1008 |
| 55 | _ | | | | ACC Thr | | | | _ | | | | | | | | 1056 |
| •• | CTT | GAC | CAA | GAA | GAG | ATG | GAG | TCC | GAG | GAT | CCA | CCG | GTC | GCC | ACC | ATG | 1104 |

| | 140 | |
|----|---|-------------|
| | Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met 355 360 365 | |
| 5 | GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val 370 380 | 1152 |
| 10 | GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu 385 390 395 400 | 1200 |
| 15 | GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys 405 410 415 | 1248 |
| | ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu 420 425 430 | 1296 |
| 20 | ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln 435 440 445 | 1344 |
| 25 | CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg 450 460 | 1392 |
| 30 | ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG GTG Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val 465 470 480 | 1440 |
| 35 | AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 490 495 | 1488 |
| | GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC ASp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn 500 505 510 | 1536 |
| 40 | TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly 515 520 525 | 1584 |
| 45 | ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val 530 540 | 1632 |
| 50 | CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 555 550 | 1680 |
| 55 | GTG CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 575 | 1728 |
| | AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG GAG TTC GTG | 1776 140 |

141

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 585 590

ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA

ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 1821

5 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
595 . 600 605

(2) INFORMATION FOR SEQ ID NO:65:

10

15

50

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 606 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr 1 5 10 15 Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser

25 20 25 30

Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu
35 40 45

Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His

30 Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His 65 70 75 80

Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu

85
90
95

Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp
100 105 110

Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln 115 120 125

Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala 130 135 140

40 Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu 145 150 155 160

Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp 165 170 175

Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu 45 180 185 190

Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser 195 200 205

Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro
210 225 220

Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly
225 230 235 240
Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg

245 250 255

Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn
250 265 270

Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met

| Leu Val Leu Asp Ser Asp Lys Arg 11e Thr Ala Ala Gln Ala Leu Ala 290 | | | | | | | | | | | 142 | ? | | | | | |
|--|-----|------------|--------------|---------------|----------------|--------------|--------------|------------|------------|------------|--------------|------------|-----------------|------------|--------------|------------|--------------|
| His Ala Tyr Phe Ala Gln Tyr His Asp Pro Asp Asp Glu Pro Val Ala 305 | | Lou | | 275 | 5 | | | | 28 | 0 | | | | 28 | 5 | | |
| 5 305 310 310 315 320 Amp Pro Tyr Asp Gln Ser Phe Glu Ser Arg Asp Leu Leu Ile Amp Glu 325 330 335 Trp Lys Ser Leu Thr Tyr Asp Glu Val Ile Ser Phe Val Pro Pro Pro Pro 340 345 350 360 10 Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met 355 360 360 Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val 370 380 Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Leu Asp Gly Gly Glu Glu Fro Trp Pro Thr Leu Lys Phe Ile Cys 405 Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Lys Phe Ile Cys 410 Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln 435 Thr Ile Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg 450 Thr Tile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val 450 Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val 485 Asp Phe Lys Glu Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 Asp Phe Lys Glu Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 Asp Phe Lys Glu Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 Soo 505 Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly 515 Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val 530 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Fro 555 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Gly Pro 550 (2) INFORMATION FOR SEO ID NO:66: 45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | | Leu | 290 | Let | ı Ası | Sei | : As | р Ly 29 | s Ar 5 | g Il | e Th | r Al | a Al | a Gl | n Al | a Le | u Ala |
| Asp Pro Tyr Asp Gln Ser Phe Glu Ser Arg Asp Leu Leu Ile Asp Glu 325 | 5 | His 305 | Ala | Туг | Phe | ≥ Ala | G1: 31: | п Ту 0 | r Hi | s As | p Pr | o Asj | As ₁ | p Glu | ı Pro | o Va | l Ala |
| Trp Lys Ser Leu Thr Tyr Asp Glu Val 11e Ser Phe Val Pro Pro Pro Pro 340 | | Asp | Pro | Tyr | Asp | Gln 325 | Se: | r Ph | e Gl | u Se | r Ar | g Ası | Let | ı Leı | ı Ile | e Asj | 320 p Glu |
| 10 · Leu Asp Gln Glu Glu Met Glu Ser Glu Asp Pro Pro Val Ala Thr Met 355 360 365 361 365 361 365 365 365 366 365 367 367 368 368 370 370 370 370 370 370 370 370 370 370 | | Trp | Lys | Ser | Leu | Thr | Ту | r Ası | o Gl | u Va | 1 Ile | 0 ∋ Sei | Phe | e Val | . Pro | 33! Pro | 5 Pro |
| Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val 370 375 380 Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu 610 Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys 405 405 410 425 430 430 435 440 445 435 440 445 435 440 445 455 460 445 450 435 465 470 455 460 475 460 475 460 475 475 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 485 480 480 485 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 485 480 480 480 485 480 480 485 480 480 480 485 480 480 480 480 480 480 480 480 480 480 | 10 | Leu | Asp | Gln | Glu | Glu | Met | : Glu | ı Se: | 34: Gl: | 5 u Asp | Pro |) Pro | Val | 350 Ala |) i Thi | r Met |
| Simple Ser S | | | | | | | | Lei | ı Phe | | | | | | | | |
| Cly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys 405 | 15 | Glu | Leu | Asp | Gly | Asp | Va] | Asn | i Gl | / His | s Lys | Phe | 380 Ser | Val | Ser | · Glv | Glu |
| ## Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu 420 | | Gly | Glu | Gly | Asp | Ala | 390 Thr | Tyr | Gly | ' Lys | Leu | 395 Thr | Leu | Lvs | Phe | Tle | 400 |
| 20 Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln 435 440 440 445 440 450 445 450 455 460 455 460 Thr Ile Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg 450 470 470 475 480 480 25 465 Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile 485 Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn 500 500 Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly 511 512 11e Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val 530 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 545 550 Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 565 Lys Asp Pro Asn. Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 580 580 580 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 600 605 (2) INFORMATION FOR SEQ ID NO:66: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | | Thr | Thr | Gly | Lys | 405 Leu | Pro | Val | Pro | Trp | 410 Pro | Thr | Leu | -, c | Thr | 415 | Cys |
| ### Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg 450 | 20 | | | | | | | | | | | | | | | | |
| Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val 465 465 470 470 470 470 470 470 470 470 470 470 | | His | Asp | 435 Phe | Phe | Lys | Ser | Ala | 440 Met | Pro | Glu | Glv | Tur | 445 | met. | Lys | GIN |
| Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 11e Glu Leu Lys Gly I1e 485 Asp Phe Lys Glu Asp Gly Asn I1e Leu Gly His Lys Leu Glu Tyr Asn 500 Tyr Asn Ser His Asn Val Tyr I1e Met Ala Asp Lys Glu Lys Asn Gly 515 I1e Lys Val Asn Phe Lys I1e Arg His Asn I1e Glu Asp Gly Ser Val 530 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro I1e Gly Asp Gly Pro 555 Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 565 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 Thr Ala Ala Gly I1e Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 (2) INFORMATION FOR SEQ ID NO:66: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 0.5 | Thr | 450 Ile | Phe | Phe | Lys | Asp | 455 Asp | Glv | Asn | Tvr | Live | 460 | 7 | GIII | GIU | Arg |
| Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn 500 Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly 515 1le Lys Val Asn Phe Lys Ile Arg His Asn Ile Gly Asp Gly Ser Val 530 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 555 Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 565 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Gly Pro 580 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 605 (2) INFORMATION FOR SEQ ID NO:66: 45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (II) MOLECULE TYPE: CDNA (IX) FEATURE: | 25 | 465 Lys | Phe (| Glu | Gly | Asp | 470 Thr | Leu | Val | Asn | Ara | 475 | Glu | Ary Tou | Ala | GIU | 480 |
| 30 Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly | | Asp I | Phe 1 | Lys | Glu | 485 Asp | Gly | Asn | Ile | Leu | 490 Glv | Hie | Tue | Leu | гув | 495 | Ile |
| The Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val 530 535 540 | 30 | Tyr A | Asn s | Ser : | 500 His . | Asn ' | Val | Tyr | Ile | 505 Met | Δla | yes | шур | neu | 510 510 | Tyr | Asn |
| Signature Sign | | Ile I | ys 1 | 515 /al / | Asn I | Phe 1 | Lys | Ile | 520 Arg | Hic | yen | Asp | пув | 525 | гу | Asn | Gly |
| Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 565 Lys Asp Pro Asn. Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 (2) INFORMATION FOR SEQ ID NO:66: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE Type: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | Δ | | | | | | | | | | | | | | | | |
| Lys Asp Pro Asn. Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 585 590 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 600 (2) INFORMATION FOR SEQ ID NO:66: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE Type: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 35 | | | | | | | | | | | | | | | | |
| Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 595 600 (2) INFORMATION FOR SEQ ID NO:66: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) Type: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE Type: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | | Lys A | .sp P | ro F | sn. G | 65 Slu 1 | vs | Ara | Agn | Deu Bio | 570 | Inr (| Gin : | Ser 1 | Ala | Leu 575 | Ser |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 40 | Thr A | la A | 5 la G | 80 Sly I | le T | hr i | Leu (| Glv | 585 Met | net Nes / | val 1 | Leu 1 | Leu (| 31u : 590 | Phe | Val |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2913 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | | | 5 | 95 | | | | (| 600 | | Asp (| Jiu i | | | rys | | |
| (A) LENGTH: 2913 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 45 | | | | | | | | | | NO:66 | 5: | | | | | |
| (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 45 | | (2 | 4) L | ENGT | H: 2 | 913 | base | na: | CS: irs | | | | | | | |
| (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | | | (1 | B) T C) S' | YPE: TRAN | nuc. DEDN | leic ESS: | aci sin | d | | | | | | | | |
| (A) NAME/KEY: Coding Sequence (B) LOCATION: 12910 | 50 | | (I |) T | OPOL | OGY: | lin | ear | | | | | | | | | |
| (B) LOCATION: 12910 | | | (ii) (ix) | MOI FE | LECUI ATURI | LE TY | PE: | CDN | A | | | | | | | | |
| (D) OTHER INFORMATION: | 55 | | (| A) N | NAME/ | KEY: | Co | ding | Seq | uenc | :e | | | | | | |
| | | | (| D) C | THEF | RINE | ORM. | 29 ATIO | N: | | | | | | | | |

143

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

| | | • | • | _ | | | | | - | _ | | | | | | | |
|----|-----|-----|-----|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5 | | | _ | GAG Glu | _ | | _ | | | | | | | | | | 48 |
| 10 | | | | GAA Glu 20 | | | | | | | | | | | | | 96 |
| 15 | | | | TCC Ser | | | | | | | | | | _ | _ | _ | 144 |
| 15 | | | | GAA Glu | | | | | | | | | | | | _ | 192 |
| 20 | | | | GAC Asp | | | | | | | | | | | | | 240 |
| 25 | | | | CCT Pro | | | | | | | | | | | | | 288 |
| 30 | | | | GGT Gly 100 | | | | | | | | | _ | | _ | _ | 336 |
| 25 | | | | CCG Pro | | | _ | | | | | | | | _ | _ | 384 |
| 35 | | | | CTT Leu | | | | | | | | | | | _ | | 432 |
| 40 | | | | ACT Thr | | | | | | | | | | | _ | _ | 480 |
| 45 | | | | CTT Leu | | | | | | | | | | | _ | | 528 |
| 50 | | | | CAC His 180 | | | | | | | | | | | | | 576 |
| 55 | | | | CCT Pro | | | | | | | | | | | | | 624 |
| 33 | TTA | GCT | CCA | GAA | GTA | CAA | AGC | TCC | GAA | GAA | TAT | ATT | CAG | CTA | TTG | AAG | 672 |

| | 144 | |
|----|---|-------------|
| | Leu Ala Pro Glu Val Gln Ser Ser Glu Glu Tyr Ile Gln Leu Leu Lys 210 215 220 | |
| 5 | AAG CTT ATT AGG TCG CCT AGC ATA CCT CAT CAG TAT TGG CTT ACG CTT Lys Leu Ile Arg Ser Pro Ser Ile Pro His Gln Tyr Trp Leu Thr Leu 230 235 240 | 720 |
| 10 | CAG TAT TTG TTA AAA CAT TTC TTC AAG CTC TCT CAA ACC TCC AGC AAA Gln Tyr Leu Leu Lys His Phe Phe Lys Leu Ser Gln Thr Ser Ser Lys 245 250 255 | 768 |
| 15 | AAT CTG TTG AAT GCA AGA GTA CTC TCT GAA ATT TTC AGC CCT ATG CTT Asn Leu Leu Asn Ala Arg Val Leu Ser Glu Ile Phe Ser Pro Met Leu 260 265 270 | 816 |
| 20 | TTC AGA TTC TCA GCA GCC AGC TCT GAT AAT ACT GAA AAC CTC ATA AAA Phe Arg Phe Ser Ala Ala Ser Ser Asp Asn Thr Glu Asn Leu Ile Lys 275 280 285 | 864 |
| 20 | GTT ATA GAA ATT TTA ATC TCA ACT GAA TGG AAT GAA CGA CAG CCT GCA Val Ile Glu Ile Leu Ile Ser Thr Glu Trp Asn Glu Arg Gln Pro Ala 290 295 300 | 912 |
| 25 | CCA GCA CTG CCT CCT AAA CCA CCA AAA CCT ACT ACT GTA GCC AAC AAC Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr Thr Val Ala Asn Asn 305 310 320 | 960 |
| 30 | GGT ATG AAT AAC AAT ATG TCC TTA CAA AAT GCT GAA TGG TAC TGG GGA Gly Met Asn Asn Met Ser Leu Gln Asn Ala Glu Trp Tyr Trp Gly 325 330 335 | 1008 |
| 35 | GAT ATC TCG AGG GAA GAA GTG AAT GAA AAA CTT CGA GAT ACA GCA GAC Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg Asp Thr Ala Asp 340 345 350 | 1056 |
| 40 | GGG ACC TTT TTG GTA CGA GAT GCG TCT ACT AAA ATG CAT GGT GAT TAT Gly Thr Phe Leu Val Arg Asp Ala Ser Thr Lys Met His Gly Asp Tyr 355 360 365 | 1104 |
| 40 | ACT CTT ACA CTA AGG AAA GGG GGA AAT AAC AAA TTA ATC AAA ATA TTT Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu Ile Lys Ile Phe 375 380 | 1152 |
| 45 | CAT CGA GAT GGG AAA TAT GGC TTC TCT GAC CCA TTA ACC TTC AGT TCT His Arg Asp Gly Lys Tyr Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser 390 395 400 | 1200 |
| 50 | GTG GTT GAA TTA ATA AAC CAC TAC CGG AAT GAA TCT CTA GCT CAG TAT Val Val Glu Leu Ile Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr 405 410 415 | 1248 |
| 55 | AAT CCC AAA TTG GAT GTG AAA TTA CTT TAT CCA GTA TCC AAA TAC CAA Asn Pro Lys Leu Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln 420 425 430 | 1296 |
| | CAG GAT CAA GTT GTC AAA GAA GAT AAT ATT GAA GCT GTA GGG AAA AAA | 1344 144 |

| | | | | | | | | | | 145 | | | | | | | |
|----|-----|-----|------------|-----|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|------|
| | Gln | Asp | Gln 435 | Val | Val | Lys | Glu | Asp 440 | Asn | Ile | Glu | Ala | Val 445 | Gly | Lys | Lys | |
| 5 | | | | | AAC Asn | | | | | | | | | | | | 1392 |
| 10 | | | | | GAA Glu | | | | | | | | | | | | 1440 |
| 15 | | | | | GAA Glu 485 | | | | | | | | | | | | 1488 |
| | | | | | CAA Gln | | | | | | | | | | | | 1536 |
| 20 | | | | | AAT Asn | | | | | | | | | | | | 1584 |
| 25 | | | | | TCT Ser | | | | | | | | | | | | 1632 |
| 30 | | | _ | | TTG Leu | | | | | | | | | | _ | | 1680 |
| 35 | | | | | AGC Ser 565 | | | | | | | | | | | | 1728 |
| | | | _ | | TTG Leu | | | | | | | | | | _ | | 1776 |
| 40 | | | | _ | TGG Trp | | _ | | | | | | | | | | 1824 |
| 45 | | | | | GAT Asp | | | | | | ~ | | | | | | 1872 |
| 50 | | | | | AGC Ser | | | | | | | | | | | | 1920 |
| 55 | | | | | ACT Thr 645 | | | | | | | | | | | | 1968 |
| 00 | TAT | GCC | TGC | TCT | GTA | GTG | GTG | GAC | GGC | GAA | GTA | AAG | CAT | TGT | GTC | ATA | 2016 |

| | 146 | |
|----|---|------|
| | Tyr Ala Cys Ser Val Val Asp Gly Glu Val Lys His Cys Val Ile 660 665 670 | |
| 5 | AAC AAA ACA GCA ACT GGC TAT GGC TTT GCC GAG CCC TAT AAC TTG TAC Asn Lys Thr Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr 675 680 685 | 2064 |
| 10 | AGC TCT CTG AAA GAA CTG GTG CTA CAT TAC CAA CAC ACC TCC CTT GTG Ser Ser Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val 690 695 700 | 2112 |
| 15 | CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC CCA GTA TAT GCA Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala 705 710 715 | 2160 |
| | CAG CAG AGG CGA CAG GAT CCA CCG GTC GCC ACC ATG GTG AGC AAG GGC Gln Gln Arg Arg Gln Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly 725 730 735 | 2208 |
| 20 | GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly 740 745 | 2256 |
| 25 | GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp 755 760 765 | 2304 |
| 30 | GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys 770 780 | 2352 |
| 35 | CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val 785 790 795 800 | 2400 |
| | CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe 805 810 815 | 2448 |
| 40 | AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe 825 830 | 2496 |
| 45 | 835 B40 845 | 2544 |
| 50 | GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu 855 860 | 2592 |
| 55 | GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His 865 870 875 880 | 2640 |
| | AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC | 2688 |

| | | | | | | | | | | 147 | | · | | | | | |
|------|-----------|------------|--------------------------|----------------------|--|----------------------|--------------------------------|---------------------|-----------|------------|--------------|------------|-----------|-----------|------------|-----------|------|
| | Asn | Val | Tyr | Ile | Met 885 | Ala | Asp | Lys | Gln | Lys 890 | Asn | Gly | Ile | Lys | Val 895 | Asn | |
| 5 | | | | | CAC His | | | | | | | | | | | | 2736 |
| 10 . | | | | | AAC Asn | | | | | | | | | | | | 2784 |
| 15 | | | | | CTG Leu | | | | | | | | | | | | 2832 |
| 13 | | | | | CAC His | | | | | | | | | | _ | _ | 2880 |
| 20 | | | | | ATG Met 965 | | | | | | TAA | | | | | | 2913 |
| 25 | | | | | FORM | | | | | NO : 6 | 5 7 : | | | | | | |
| 30 | | | (A) (B) (C) (D) | LENG TYPI STRA | NCE (GTH: E: an ANDEI OLOG! | 970 mino ONESS | amin acio 3: s: inean | no ad i ingle | cids e | | | | | | | | |
| 35 | | (7 | /) FI | RAGMI | ENT : | TYPE | : int | terna | al | Q ID | NO: | 67: | | | | | |
| 40 | 1 | | | | Gly 5 Asp | | | | | 10 | | | A | _ | 15 | | |
| | Asn | Lys | Gly 35 | 20 Ser | Leu | Val | Ala | Leu 40 | 25 Gly | Phe | Ser | Asp | Gly 45 | 30 Gln | Glu | Ala | |
| 45 | | 50 | | | Ile Phe | | 55 | | | | | 60 | | | | | |
| | 65 Lys | Ile | Ser | Pro | Pro 85 | 70 Thr | Pro | Lys | Pro | Arg 90 | 75 Pro | Pro | Arg | Pro | Leu 95 | 80 Pro | |
| 50 | | | | 100 | Ser Asp | | - | | 105 | | _ | | | 110 | | | |
| | | | 115 | | Ile | | Leu | 120 | | | | | 125 | | | | |
| 55 | Glu | 130 Cys | Ser | Thr | Leu | Tyr | 135 Arg | Thr | Gln | Ser | Ser | 140 Ser | Asn | Leu | Ala | Glu | |

| | | | | | | | 14 | 48 | | | | | | | |
|----|----|-------------------|--|----|---|--|-----|------|-----|------------|-------|------|-----|------|--------------|
| | 45 | | | 15 | 0 | | | | 155 | 5 | | | | | 160 |
| | | | | | | | | | | | | | | | 160 u Met |
| 5 | | | | | | | | | | | | | | | u Asp |
| | | | | | | | | | | | | lu | Met | : 11 | e Ser |
| 40 | | | | | | | | | | | e G | ln : | | | u Lys |
| 10 | | | | | | | | | | Ту | r Tı | | | | r Leu |
| | | | | | | | | eu . | Ser | G1 | | | | | 240 Lys |
| 15 | | | | | | | r G | lu : | | | | | | | Leu |
| | | | | | | | | | | | | n I | Leu | Ιle | . Lys |
| 20 | | | | | | | | | | | ı Ar | g | | | Ala |
| 20 | | | | | | | | | | Thi | va va | | | | Asn 320 |
| | | sn As | | | | | | | | | | | | | |
| 25 | | r Ar | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| 30 | | r Le | | | | | | | | | | | | | |
| | | p Gly | | | | | | | | | | | | | |
| | | u Lei | | | | | | | | | | | | | |
| 35 | | s Leu 420 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| 40 | | ı Tyr | | | | | | | | | | | | | |
| | | Glu Ile | | | | | | | | | | | | | |
| | | lle Thr | | | | | | | | | | | | | |
| 45 | | Thr 500 Gly | | | | | | | | | | | | | |
| | | Lys | | | | | | | | | | | | | |
| 50 | | Asp | | | | | | | | | | | | | |
| | | Asn | | | | | | | | | | | | | |
| 55 | | Tyr 580 | | | | | | | | | | | | | |
| 55 | | 580 Glu | | | | | | | | | | | | | |
| | | | | | - | | | | J. | ~ ~ | -SP | 110 | . 1 | уг с |)CT |

149

| | | | 595 | | | | | 600 | | | | | 605 | | | |
|----|--------------|--------------|------|-----------|------|-------|------|-------------|-------|-------|--------------|----------|-------|-----|------------|----------|
| | Len | Val | | Asp | Asn | Glu | Asp | | Pro | His | His | Δen | | Lys | Thr | Trn |
| | | 610 | | | 1.00 | | 615 | 204 | | **** | | 620 | Olu | Lys | 1111 | 111 |
| | Asn | | Glv | Ser | Ser | Asn | | Asn | Lvs | Ala | Glu | | Len | Leu | Ara | Glv |
| 5 | 625 | | 1 | | | 630 | | | -1- | | 635 | | | | •••• | 640 |
| - | | Ara | Asp | Glv | Thr | | Leu | Val | Ara | Glu | | Ser | Lvs | Gln | Glv | |
| | | 3 | | 1 | 645 | | | | J | 650 | | | -7- | | 655 | -1- |
| | Tyr | Ala | Cys | Ser | Val | Val | Val | qaA | Gly | | Val | Lys | His | Cys | | Ile |
| | • | | • | 660 | | | | - | 665 | | | • | | 670 | | |
| 10 | Asn | Lys | Thr | Ala | Thr | Gly | Tyr | Gly | Phe | Ala | Glu | Pro | Tyr | Asn | Leu | Tyr |
| | | | 675 | | | | | 680 | | | | | 685 | | | _ |
| | Ser | Ser | Leu | Lys | Glu | Leu | Val | Leu | His | Tyr | Gln | His | Thr | Ser | Leu | Val |
| | | 690 | | | | | 695 | | | | | 700 | | | | |
| | Gln | His | Asn | Asp | Ser | Leu | Asn | Val | Thr | Leu | Ala | Tyr | Pro | Val | Tyr | Ala |
| 15 | 705 | | | | | 710 | | | | | 715 | | | | | 720 |
| | Gln | Gln | Arg | Arg | | Asp | Pro | Pro | Val | | Thr | Met | Val | Ser | | Gly |
| | | | | | 725 | | A, | | | 730 | | | | • | 735 | |
| | Glu | Glu | Leu | | Thr | Gly | Val | Val | | Ile | Leu | Val | Glu | Leu | Asp | Gly |
| 00 | _ | | _ | 740 | | _ | | _ | 745 | | | | | 750 | | |
| 20 | Asp | Val | | Gly | Hıs | Lys | Phe | | Val | Ser | GIÀ | Glu | - | Glu | Gly | Asp |
| | n 1 - | m\ | 755 | 01 | * | * | m) | 760 | • | D1 | T 7 - | | 765 | _, | a 1 | - |
| | Ala | 770 | туг | GIY | гÀг | Leu | | ьеи | гав | Pne | rre | - | Thr | Thr | GIY | ьуs |
| | T 011 | | 1101 | Dwa | T | Dwo | 775 | T | 17-7 | mh se | mh | 780 | mb | Tyr | 01 | 17.3 |
| 25 | 785 | PIO | val | PIO | тър | 790 | 1111 | ьец | val | IIII | 795 | neu | 1111 | TAT | GIY | 800 |
| | | Cvs | Phe | Ser | Ara | | Pro | Δsn | His | Met | | Gln | ніе | qaA | Dhe | - |
| | 0211 | C , D | | | 805 | - 7 - | | тор | ***** | 810 | - | 0111 | 111.5 | дор | 815 | 1110 |
| | Lvs | Ser | Ala | Met | | Glu | Glv | Tyr | Val | | | Ara | Thr | Ile | | Phe |
| | • | | | 820 | | | • | • | 825 | | | | | 830 | | |
| 30 | Lys | Asp | Asp | Gly | Asn | Tyr | Lys | Thr | Arg | Ala | Glu | Val | Lys | Phe | Glu | Gly |
| | | | 835 | | | | | 840 | | | | | 845 | | | |
| | Asp | Thr | Leu | Val | Asn | Arg | Ile | Glu | Leu | Lys | Gly | Ile | Asp | Phe | Lys | Glu |
| | | 850 | | | | | 855 | | | | | 860 | | | | |
| | | Gly | Asn | Ile | Leu | | His | Lys | Leu | Glu | | Asn | Tyr | Asn | Ser | |
| 35 | 865 | | | | | 870 | | | | | 875 | | | | _ | 880 |
| | Asn | Val | Tyr | Ile | | Ala | Asp | Lys | Gln | | Asn | Gly | Ile | Lys | | Asn |
| | 51. . | . | *1. | • | 885 | | -1. | ~3 | _ | 890 | _ | | | _ | 895 | _ |
| | Pne | гуѕ | 11e | | ніѕ | Asn | 11e | GIU | | GIÄ | Ser | Val | Gin | Leu | Ala | Asp |
| 40 | 114 - | (T) | a1 | 900 | 2 | mh | D | -1 - | 905 | | ~ 3 | 5 | **- 3 | 910 | | D |
| 40 | HIS | Tyr | 915 | GIII | Asn | Int | Pro | 920 | GIY | Asp | GIY | Pro | 925 | Leu | Leu | PIO |
| | yen | λen | | Tur | T.Au | Ser | Thr | | Cor | λ1- | Ton | 802 | | Asp | Dro | λαπ |
| | тэр | 930 | 1113 | 171 | Deu | Ser | 935 | GIII | Ser | Ala | цеu | 940 | цув | жыр | PIO | ASII |
| | G] 11 | | Ara | Asp | His | Met | | Len | Len | Glu | Phe | | Thr | Ala | Ala | Glv |
| 45 | 945 | _,_ | 3 | | | 950 | | | | | 955 | 741 | ~*** | | | 960 |
| - | | Thr | Leu | Gly | Met | | Glu | Leu | Tyr | Lys | | | | | | |
| | | | | • | 965 | • | | | - | 970 | | | | | | |
| | | | | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:68:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1788 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 55 (D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA (ix) FEATURE:

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1785 5

(D) OTHER INFORMATION:

| 10 ATG GGC AAC GCC GCC GCC GCC AAG AAG GGC AGC GAG CAG GAG AGC GTG Met Gly Asn Ala Ala Ala Ala Ala Lys Lys Gly Ser Glu Gln Glu Ser Val 1 5 AAA GAG TTC CTA GCC AAA GCC AAG GAA GAT TTC CTG AAA AAA TGG GAA Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu 20 25 GAC CCC TCT CAG AAT ACA GCC CAG TTG GAT CAG TTT GAT AGA ATC AAG Asp Pro Ser Gln Asn Thr Ala Gln Leu Asp Gln Phe Asp Arg Ile Lys 45 ACC CTT GGC ACC GGC TCC TTT GGG CGA GTG ATG CTG GTG AAG CAC AAG Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys 50 GAG AGT GGG AAC CAC TAC GCC ATG AAG ATC TTA GAC AAG CAG AAG GTG Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val 65 GAG AGT GAG CTA AAG CAG ATC GAG CAC ACT CTG AAT GAG AAG CGC ATC CTG Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asn Glu Lys Arg Ile Leu 85 GAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA CAG CAC AATC CTG Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu 85 CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA CTC CTC TCC 85 GAC AAC TCA AAC CTG TAC ATG GTC AAA CTT GAA CTT GAA TTC TCC TTC AAG ASp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu 115 ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGG GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 ATG TTC TCC CAC CTA CGG CGG ATC GTC ACC TTT GAG TAT CTG CAC CTC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CGT TTC TAC GG GGG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CCAG CAG GCC TAT CTA CAG GGG ACC CTG AAG CCC GAG AAT CTT CTC ATC GAC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CCAG CAG GCC TAT CTA CAG GGG ACC CTG AAG CCC GAG AAT CTT CTC ATC GAC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CCAG CAG GCC TAT CTA CAG GGG ACC CTG AAG CCC GAG AAT CTT CTC ATC GAC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CCAG CAG GCC TAT ATT CAG CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC ACG CAG GCC TAT ATT | | | | (| xi) | SEC | QUEN | CE D | ESCR | IPTI | ON: | SEQ | ID | NO: | 68: | | | | | | | |
|--|----|------------|------------|-----|--------------|-----------------|--------------|------------|------------|------------|---------|------------|------------|----------|------------|------------|------------|------------|------------|-----------|-----|---|
| 20 25 25 26 26 27 27 28 28 28 29 29 29 29 29 29 29 29 29 29 29 29 29 | 10 | 1 | L | - | | | 5 | 5 | Lu A | ra D | λs π | ys (| 0 17A | Ser | Glı | u Gl: | n Gl | u Se | er 5 | Val | 48 | 3 |
| ACC CTT GGC ACC GGC TCC TTT GGG CGA GTG ATG CTG GTG AAG CAC AAG ACC CTT GGC ACC GGC TCC TTT GGG CGA GTG ATG CTG GTG AAG CAC AAG Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys 50 GAG AGT GGG AAC CAC TAC GCC ATG AAG ATC TTA GAC AAG CAG AAG GTG Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val 65 70 GTG AAG CTA AAG CAG ATC GAG CAC ACT CTG AAT GAG AAG CGC ATC CTG 85 CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA TGAG AAG CGC ATC CTG 90 GAC AAC TCA AAC CTG TAC ATC GTC ATG GTC AAA CTT GAA TTC TCC TTC AAG ASp Asn Ser Asn Leu Tyr Met Val Lys Leu Glu Phe Ser Phe Lys 100 GAC AAC TCA AAC CTG TAC ATG GTC ATG GAG TAT GTA GCT GGT GGC GAG ASp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu 115 ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TC AGC GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 CGT TC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 140 CGT TC TC CAC CTA TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 140 CGT GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 140 CGG CAG CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 140 CGG CAG CAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC Arg Phe Tyr Ala Ala Gln Ile Val Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG CAG CTT ATT CAG CGG GAC TTG AGC CTC GAG AAT CTT CTC ATC AAG CAG CAG CTC ATC TAC CAG GAC CTC GAG CCC CAG CCC CAG CCC ATC CAG CAG CTC ATC TAC CAG GAC CTC CAG CCC CAG CCC CAG CCC ATC CAG CAG CTC ATC TAC CAG GAC CTC CAG CCC CAG CCC CAG CCC CAG CCC CAG CCC CAC CCC CAG CCC CAC CCC CAG CCC CAC CCC CAG CCC CA | 15 | | | | | 20 | | | U A. | נת בי | 25 | iu A | sp . | Phe | Let | ı Ly: | s Ly 30 | s Tr | p | Glu | 96 | ; |
| 25 | 20 | | | | 35 | | | | ı nı | 40 | .11 116 | u A | sp (| 31n | Phe | Asp 45 |) Ar | g Il | e | Lys | 144 | |
| 65 70 70 70 75 75 75 80 1 1 2 80 80 80 80 80 80 80 80 80 80 80 80 80 | 25 | | 5 | 0 | _ | | - J <u>-</u> | , 50 | 55 | e GI | y Ar | g va | al M | let | Leu 60 | Val | . Lys | Hi: | s 1 | Lys | 192 | |
| CAG GCC GTC AAC TTC CCG TTC CTG GTC AAA CTT GAA TTC TCC TTC AAG 336 Gln Ala Val Asn Phe Pro Phe Leu Val Lys Leu Glu Phe Ser Phe Lys 110 GAC AAC TCA AAC CTG TAC ATG GTC ATG GAG TAT GTA GCT GGT GGC GAG ASP ASP ASP ASP Leu Arg Arg 11e Gly Arg Phe Ser Glu Pro His Ala 130 ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGC GAG CCC CAT GCC Arg Phe Ser His Leu Arg Arg 11e Gly Arg Phe Ser Glu Pro His Ala 130 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 160 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 160 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Arg Phe Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 175 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | 20 | 65 | | | • | | | 70 | . AI | a Me | с гу | S 1. | .е L 7 | eu 5 | Asp | Ьуs | Gln | Lys | <i>]</i> 8 | /al 30 | 240 | |
| GAC AAC TCA AAC CTG TAC ATG GTC ATG GLU Tyr Val Ala Gly Gly Glu 125 ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGC GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 150 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | 30 | | - | | | -1- | 85 | | . 011 | ı nı; | s Ini | 90 90 | u A | sn | Glu | Lys | Arg | 11e 95 | ≥ L | eu | 288 | |
| ATG TTC TCC CAC CTA CGG CGG ATT GGA AGG TTC AGC GAG CCC CAT GCC Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 130 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 145 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 56 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | 35 | | | | | 100 | | | 7 1110 | . nec | 105 | г гу | s Le | eu (| Glu | Phe | Ser 110 | Phe | L | ys | 336 | |
| 130 135 135 140 CGT TTC TAC GCG GCG CAG ATC GTC CTG ACC TTT GAG TAT CTG CAC TCC ATC ATC Phe Glu Tyr Leu His Ser 150 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | 40 | | | 1 | .15 | | 204 | -71 | nec | 120 | мет | GI. | u Ty | r \ | Val | Ala 125 | Gly | Gly | G. | lu | 384 | |
| 145 150 150 155 160 50 CTG GAC CTC ATC TAC CGG GAC CTG AAG CCC GAG AAT CTT CTC ATC GAC Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | 45 | | 13 | 0 | | | | •••9 | 135 | 116 | GIY | Arg | 3 Ph | e 5 | Ser 140 | Glu | Pro | His | A] | la | 432 | |
| Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 165 170 175 CAG CAG GGC TAT ATT CAG GTG ACA GAC TTC GGT TTT GCC AAG CGT GTG 576 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val | | 145 | | | - | | | 150 | 116 | vai | Leu | Thi | 15 | e G 5 | lu ' | Tyr | Leu | His | Se 16 | er 50 | 480 | |
| 180 The Asp Phe Gly Phe Ala Lys Arg Val | 50 | | | | | | 165 | 9 | rap | ьец | Lys | 170 | GI | uA | .sn I | Leu 1 | Leu | Ile 175 | As | p | 528 | |
| | 55 | CAG Gln | CAG Gln | G G | GC 1 ly 1 | AT Yr .80 | ATT Ile | CAG Gln | GTG Val | ACA Thr | Asp | TTC Phe | GG: Gly | r T | TT (| Ala I | ys i | CGT Arg | GT Va | G 1 | 576 | |

| E | | GGC Gly | | | | | | | | | | | 624 |
|----|---|-------------------|---|---|---|---|---|--|---|---|---|---|------|
| 5 | | ATT Ile 210 | | | | | | | | | | | 672 |
| 10 | | GGA Gly | | | | | | | | | | | 720 |
| 15 | | GAC Asp | | | | _ | | | | | | _ | 768 |
| 20 | | TTC Phe | | | | | | | | | | | 816 |
| 25 | | CTG Leu | | | | | | | | | | | 864 |
| | | AAT Asn 290 | | | | | | | | | | | 912 |
| 30 | | ATC Ile | | | | | | | | | | | 960 |
| 35 | _ | CCT Pro | _ | | | | | | | | _ | _ | 1008 |
| 40 | | GTC Val | | | _ | | | | | | | _ | 1056 |
| 45 | | GCC Ala | | | _ | _ | _ | | _ | _ | | _ | 1104 |
| | | GTT Val 370 | | | | | | | | | | | 1152 |
| 50 | | GAG Glu | | | | | | | | | | | 1200 |
| 55 | _ | TGC Cys | | _ | | | | | | | | | 1248 |

152

| 5 | ACT CTC ACT TAT GGT GTT CAA TGC TTT TCT AGA TAC CCA GAT CAT ATG Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met 420 425 430 | 1296 |
|----|---|------|
| | AAA CAG CAT GAC TTT TTC AAG AGT GCC ATG CCC GAA GGT TAT GTA CAG Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln 435 440 445 | 1344 |
| 10 | GAA AGA ACT ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT GCT Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala 450 455 460 | 1392 |
| 15 | GAA GTC AAG TTT GAA GGT GAT ACC CTT GTT AAT AGA ATC GAG TTA AAA Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys 465 470 480 | 1440 |
| 20 | 485 490 495 | 1488 |
| 25 | 500 FOST THE MET ALA ASP Lys Pro Lys 505 510 | 1536 |
| | 515 Eys 11e Arg His Asn Ile Lys Asp Gly 525 | 1584 |
| 30 | AGC GTT CAA TTA GCA GAC CAT TAT CAA CAA AAT ACT CCA ATT GGC GAT 1 Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp 530 540 | .632 |
| 35 | GGC CCT GTC CTT TTA CCA GAC AAC CAT TAC CTG TCC ACG CAA TCT GCC Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala 550 555 560 | 680 |
| 40 | CTT TCC AAA GAT CCC AAC GAA AAG AGA GAT CAC ATG ATC CTT CTT GAG Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu Glu 565 570 575 | 728 |
| 45 | TTT GTA ACA GCT GCT GGG ATT ACA CAT GGC ATG GAT GAA CTA TAC AAA Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys 580 590 | 776 |
| | CCT CAG GAG TAA Pro Gln Glu 1 595 | 788 |
| 50 | (2) INFORMATION FOR SEQ ID NO:69: | |
| 55 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 595 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single | |

(C) STRANDEDNESS: single

153

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Gly Asn Ala Ala Ala Lys Lys Gly Ser Glu Gln Glu Ser Val 10 10 Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu Lys Lys Trp Glu 25 Asp Pro Ser Gln Asn Thr Ala Gln Leu Asp Gln Phe Asp Arg Ile Lys 40 Thr Leu Gly Thr Gly Ser Phe Gly Arg Val Met Leu Val Lys His Lys 15 Glu Ser Gly Asn His Tyr Ala Met Lys Ile Leu Asp Lys Gln Lys Val 70 Val Lys Leu Lys Gln Ile Glu His Thr Leu Asn Glu Lys Arg Ile Leu 85 90 Gln Ala Val Asn Phe Pro Phe Leu Val Lys Leu Glu Phe Ser Phe Lys 20 105 Asp Asn Ser Asn Leu Tyr Met Val Met Glu Tyr Val Ala Gly Gly Glu 120 Met Phe Ser His Leu Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala 25 135 Arg Phe Tyr Ala Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser 150 155 Leu Asp Leu Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp 170 165 30 Gln Gln Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val 180 185 Lys Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro 200 Glu Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp Ala 35 210 215 220 Leu Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro Phe Phe 230 235 Ala Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser Gly Lys Val 250 40 Arg Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp Leu Leu Arg Asn 260 265 Leu Leu Gln Val Asp Leu Thr Lys Arg Phe Gly Asn Leu Lys Asp Gly 280 Val Asn Asp Ile Lys Asn His Lys Trp Phe Ala Thr Thr Asp Trp Ile 45 295 300 Ala Ile Tyr Gln Arg Lys Val Glu Ala Pro Phe Ile Pro Lys Phe Lys 310 Gly Pro Gly Asp Thr Ser Asn Phe Asp Asp Tyr Glu Glu Glu Ile 325 330 50 Arg Val Ser Ile Asn Glu Lys Cys Gly Lys Glu Phe Thr Glu Phe Gly 345 Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile 360 Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val Ser 55 375 Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe

| | | | | | | | | 154 | | | | | | | |
|----|------------------------|----------------------|-----------------|----------------|------------|--------------|-------------|------------|---------------|--------------|--------------|----------------|--------------|------------|-----|
| | 385 | | | 390 | | | | | 305 | | | | | | |
| | Ile Cy | s Thr T | hr Gly 405 | Lys | Leu | Pro | Val | Pro | 395 Trp | Pro | Thr | Leu | Val | 400 Thr | |
| 5 | Thr Le | u Thr T | yr Gly | Val | Gln | Cys | Phe | Ser | Arg | Tyr | Pro | Asp | 415 His | Met | |
| | Lys Gl: | n His A | zo ∋p Phe | Phe | Lys | Ser | 425 Ala | Met | Pro | Glu | Glv | 430 | บาโ | C1- | |
| | Glu Ar | 435 g Thr I: O | le Phe | Tyr | Lys | 440 Asp | Asn | Gly | 7.00 | <i>m</i> | 445 | -, | val | GIN | |
| 10 | 450 Glu Val |) l Lys Pl | ne Glu | Glv | 455 | mb | т. | GIY | ASII | 1yr 460 | ьув | Thr | Arg | Ala | |
| | 465 Gly 11e | l Lys Pl | | 470 | - Tap | Int | Leu | Val | Asn 475 | Arg | Ile | Glu | Leu | Lys 480 | |
| | D | Asp Ph | 485 | GLu | Asp | Gly | Asn | Ile 490 | Leu | Gly | His | Lys | Met | Glu | |
| 15 | Tyr Asn | Tyr As | n Ser 0 | His | Asn | Val | Tyr 505 | Ile | Met | Ala | Asp | Lys | Pro | Lys | |
| | Asn Gly | Ile Ly 515 | s Val | Asn | Phe | Lys | Ile | Arg | His | Asn | Ile | 510 Lys | Asp | Gly | |
| | Ser Val 530 | Gln Le | u Ala | Asp 1 | His | 520 Tyr | Gln | Gln | Asn | Thr | 525 Pro | Ile | Glv | Δen | |
| 20 | Gly Pro 545 | Val Le | ı Leu | Pro A | 535 Asp | Asn | His | Tvr | I.em | 540 | Th. | a1 | o., | льр | |
| | 545 Leu Ser | Lys As | o Pro | 550 Asn (| :11: | Lve | 7 | ~ / L | 555 | | TIIL | GIN | ser . | Ala 560 | |
| | Phe Val | Thr Al: | 565 | د داد | | - y - S | Arg | 570 | H1S | Met . | Ile | Leu | Leu (575 | Glu | |
| 25 | Phe Val | 580 |) | GIY I | .ie ' | rnr . | His 585 | Gly : | Met i | Asp (| 31u | Leu ' 590 | Tyr] | Гуs | |
| | Pro Gln | 595 | | | | | | | | | | - | | | |
| | | (2) IN | FORMA | rion | FOR | SEO | TD i | NTO - 74 | | | | | | | |
| 30 | (i |) SEQUE | | | | | | |) : | | | | | | |
| | · | (A) LEN | GTH: 2 | 181 | base | na i | irs | | | | | | | | |
| 35 | | (B) TYP | ANDEDN | ESS: | sin | d gle | | | | | | | | | |
| 33 | | (D) TOP | OLOGY: | line | ear | | | | | | | | | | |
| | (i (i: | i) MOLE x) FEAT | CULE T | YPE: | CDN. | A | | | | | | | | | |
| 40 | | | | | | | | | | | | | | | |
| | | (A) NAM | ALION | : 1 | .21 | 78 | uenc | e | | | | | | | |
| | | (D) OTI | | | | | | | | | | | | | |
| 45 | |) SEQUE | | | | | | | | | | | | | |
| | ATG AGC G | AC GTG | GCT AT | T GT | G AA | AG GA | AG G | GT TO | G CI | rg ca | C A | AA CO | a Go | ıcı | 4.0 |
| | Met Ser A | sp val | Ala [] 5 | le Va | l Ly | rs G] | lu G: 10 | гу Тъ | TP Le | u Hi | s Ly | /s Ar | g G1 | у. | 48 |
| 50 | GAG TAC A | TC AAG | ACC TO | G CG | g cc | 'A CC | | | | | | 15 | | | |
| | Glu Tyr I | le Lys 20 | Thr Tr | p Ar | g Pr | O AL | 9 1 | r Ph | C CT le Le | C CT u Le | C AA u Ly | AG AA 's As | T GA n As | T. p | 96 |
| | | | | | | 25 | • | | | | 30 |) | | | |
| 55 | GGC ACC T Gly Thr P | he Ile | GC TA Gly Ty | C AAC r Lys | GA Gl: | G CG u Ar | G CC | G CA | G GA | T GT | G GA | C CA | A CG | Т | 144 |
| | 3. | 5 | | | 40 | _ | J | - 01 | no | 45 | . AS | b GT | n Ar | g | |
| | | | | | | | | | | | | | | | |

| 5 | | | | CTC Leu | | | | | _ | | | | | | | | 192 |
|----|-----|------------|------------|-------------------|-----|-----|------------|------------|------------|-----|-----|------------|------------|------------|-----|-----|------|
| - | | | | CCC Pro | | | - | | | | | | | | | | 240 |
| 10 | | | | ATC Ile | | | | | | | | | | | | | 288 |
| 15 | | | | ACA Thr 100 | | | | | | - | _ | | | | | | 336 |
| 20 | | | | GAG Glu | | | | | | | | | | | | | 384 |
| 25 | | | | GAA Glu | | | | | | | | | | | | | 432 |
| | | | | AAC Asn | | | | | | | | | | | | | 480 |
| 30 | | | | GTG Val | | | | | | | | | | | | | ·528 |
| 35 | Ala | Met | Lys | ATC Ile 180 | Leu | Lys | Lys | Glu | Val 185 | Ile | Val | Ala | Lys | Asp 190 | Glu | Val | 576 |
| 40 | Ala | His | Thr 195 | CTC Leu | Thr | Glu | Asn | Arg 200 | Val | Leu | Gln | Asn | Ser 205 | Arg | His | Pro | 624 |
| 45 | Phe | Leu 210 | Thr | GCC Ala | Leu | Lys | Tyr 215 | Ser | Phe | Gln | Thr | His 220 | Asp | Arg | Leu | Cys | 672 |
| | | | | GAG Glu | | | | | | | | | | | | | 720 |
| 50 | | | | GTG Val | | | | | | | | | | | | | 768 |
| 55 | | | | GCC Ala 260 | | | | | | | | | | | | | 816 |

| 5 | 275 | 280 | • | Asp Gly His Ile 285 | 864 |
|----|---|---|---|---------------------------------------|------|
| | AAG ATC ACA GAC Lys Ile Thr Asp 290 | TTC GGG CTG TGC Phe Gly Leu Cys 295 | AAG GAG GGG ATC 2 Lys Glu Gly Ile 1 300 | AAG GAC GGT GCC Lys Asp Gly Ala | 912 |
| 10 | 305 | 310 | CCT GAG TAC CTG (Pro Glu Tyr Leu F | ula Pro Glu Val 320 | 960 |
| 15 | | 325 | GCA GTG GAC TGG T Ala Val Asp Trp T 330 | rp Gly Leu Gly 335 | 1008 |
| 20 | 340 | nee nee cys | GGT CGC CTG CCC T Gly Arg Leu Pro P 345 | he Tyr Asn Gln 350 | 1056 |
| 25 | 355 | 360 | | lu Ile Arg Phe 55 | 1104 |
| 0. | 370 | 375 | AAG TCC TTG CTT TO Lys Ser Leu Leu Se 380 | er Gly Leu Leu | 1152 |
| 30 | AAG AAG GAC CCC A Lys Lys Asp Pro L 385 | 390 | 395 Gly Gly Ser Gl | u Asp Ala Lys 400 | 1200 |
| 35 | | os | tia Gly He Val Tr 410 | p Gln His Val 415 | 1248 |
| 40 | TAC GAG AAG AAG CT Tyr Glu Lys Lys Le 420 | - Del 110 PIO P | TC AAG CCC CAG GT he Lys Pro Gln Va 25 | C ACG TCG GAG l Thr Ser Glu 430 | 1296 |
| 45 | ACT GAC ACC AGG TR Thr Asp Thr Arg Ty 435 | AT TTT GAT GAG G T Phe Asp Glu G 440 | AG TTC ACG GCC CAG lu Phe Thr Ala Glr 445 | Met Ile Thr | 1344 |
| | ATC ACA CCA CCT GA Ile Thr Pro Pro As 450 | C CAA GAT GAC A p Gln Asp Asp S 455 | GC ATG GAG TGT GTG er Met Glu Cys Val 460 | GAC AGC GAG Asp Ser Glu | 1392 |
| 50 | CGC AGG CCC CAC TT Arg Arg Pro His Ph 465 | C CCC CAG TTC TO e Pro Gln Phe Se 470 | CC TAC TCG GCC AGC er Tyr Ser Ala Ser 475 | AGC ACG GCC Ser Thr Ala 480 | 1440 |
| 55 | TCG GAT CCA CCG GTG Ser Asp Pro Pro Va: 489 | - wit Met As | G AGC AAG GGC GAG 1 Ser Lys Gly Glu 490 | | 1488 |

| 5 | - | | GTG Val 500 | | | | | | | | 1536 |
|----|---|---|-------------------|--|--|--|--|--|---|---|------|
| 3 | - | | AGC Ser | | | | | | | | 1584 |
| 10 | | | CTG Leu | | | | | | | | 1632 |
| 15 | | - | CTC Leu | | | | | | | | 1680 |
| 20 | | | GAC Asp | | | | | | | | 1728 |
| 25 | | | TAC Tyr 580 | | | | | | | | 1776 |
| | | | ACC Thr | | | | | | | | 1824 |
| 30 | | | GAG Glu | | | | | | | _ | 1872 |
| 35 | | | AAG Lys | | | | | | | _ | 1920 |
| 40 | | | AAG Lys | | | | | | _ | | 1968 |
| 45 | | | GAG Glu 660 | | | | | | | _ | 2016 |
| | | | ATC Ile | | | | | | | | 2064 |
| 50 | | | CAG Gln | | | | | | | | 2112 |
| 55 | | | CTG Leu | | | | | | | | 2160 |

158

ATG GAC GAG CTG TAC AAG TAA Met Asp Glu Leu Tyr Lys 2181 5 (2) INFORMATION FOR SEQ ID NO:71: (i) SEQUENCE CHARACTERISTICS: 10 (A) LENGTH: 726 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71: 20 Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp 25 Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg 25 Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys 55 Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg 75 30 85 Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys 105 Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn 35 120 Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg 135 140 Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr 150 40 Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr 165 170 Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val 185 Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro 45 200 Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys 215 Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser 220 230 Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu 50 250 Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr 265 Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile 55 280 Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

| | | 290 | | | | | 205 | | | | | 200 | | | | |
|-----|------------|-------|------|------|------------|------------|------|------------|------|------------|-----|-------------|-----------|----------|------------|----------|
| | Thr | | Luc | Thr | Phe | Cvo | 295 | Th~ | Dro | C1 | Т | 300 | 77. | Dana | a 1 | T7- 7 |
| | 305 | MCC | Буз | 1111 | FIIC | 310 | GIY | THE | PIO | GIU | 315 | Leu | Ald | PIO | GIU | 320 |
| | | Glu | Asp | Asn | Asp | | Glv | Δra | Δla | Val | | Trn | Ттъ | Gly | T.em | |
| 5 | | | | | 325 | -/- | 01, | 9 | niu | 330 | ASP | ııp | ııp | Gry | 335 | GIY |
| - | Val | Val | Met | Tyr | Glu | Met | Met | Cvs | Glv | | Leu | Pro | Phe | Tvr | | Gln |
| | | | | 340 | | | | - 2 | 345 | 5 | | | | 350 | | |
| | Asp | His | Glu | Lys | Leu | Phe | Glu | Leu | Ile | Leu | Met | Glu | Glu | | Arq | Phe |
| | | | 355 | | | | | 360 | | | | | 365 | | | |
| 10 | Pro | Arg | Thr | Leu | Gly | Pro | Glu | Ala | Lys | Ser | Leu | Leu | Ser | Gly | Leu | Leu |
| | | 370 | | | | | 375 | | | | | 380 | | | | |
| | Lys | Lys | Asp | Pro | Lys | Gln | Arg | Leu | Gly | Gly | Gly | Ser | Glu | Asp | Ala | Lys |
| | 385 | | | | | 390 | | | | | 395 | | | • | | 400 |
| 4.5 | Glu | Ile | Met | Gln | His | Arg | Phe | Phe | Ala | | Ile | Val | Trp | Gln | His | Val |
| 15 | _ | -1 | _ | _ | 405 | _ | _ | _ | | 410 | _ | | | | 415 | |
| | lyr | GIU | гÀг | | Leu | ser | Pro | Pro | | Lys | Pro | GIn | Val | | Ser | Glu |
| | Th. | λαν | Th∽ | 420 | Tyr | Dho | 7 ~~ | 61. | 425 | Db = | mh | 71 - | 01 | 430 | T1. | mb |
| | 1111 | мър | 435 | Arg | TYL | Pne | Asp | 440 | Giu | Pne | Inr | Ala | 445 | Met | TTE | Thr |
| 20 | Tle | Thr | | Pro | Asp | Gln | Asn | | Ser | Met | Glu | Cvs | | Δen | Ser | Glu |
| | | 450 | | | | | 455 | p | 501 | | O1u | 460 | Vu. | nop | OCI | Olu |
| | Arg | Arg | Pro | His | Phe | Pro | | Phe | Ser | Tyr | Ser | | Ser | Ser | Thr | Ala |
| | 465 | _ | | | | 470 | | | | - | 475 | | | | | 480 |
| | Ser | Asp | Pro | Pro | Val | Ala | Thr | Met | Val | Ser | Lys | Gly | Glu | Glu | Leu | Phe |
| 25 | | | | | 485 | | | | | 490 | | | | | 495 | |
| | Thr | Gly | Val | | Pro | Ile | Leu | Val | Glu | Leu | Asp | Gly | Asp | Val | Asn | Gly |
| | | | | 500 | _ | | | | 505 | | | | | 510 | | |
| | His | Lys | | Ser | Val | Ser | Gly | | Gly | Glu | Gly | Asp | | Thr | Tyr | Gly |
| 30 | T 1 | T 011 | 515 | T | T | Dh. | T1. | 520 | ml | m 1 | ~1 | . . | 525 | 5 | **- 7 | D |
| 30 | гуѕ | 530 | IIII | Leu | Lys | Pne | 535 | сув | inr | Thr | GIY | | Leu | Pro | vai | Pro |
| | Trn | | Thr | T.em | Val | Thr | | Len | Thr | Tree | Glv | 540 | Gln | Cvc | Dhe | Car |
| | 545 | | | | | 550 | **** | LCu | 1111 | LYL | 555 | Vai | GIII | Cys | FIIC | 560 |
| | | Tyr | Pro | Asp | His | | Lvs | Gln | His | Asp | | Phe | Lvs | Ser | Ala | |
| 35 | _ | • | | • | 565 | | • | | | 570 | | | -2- | - | 575 | |
| | Pro | Glu | Gly | Tyr | Val | Gln | Glu | Arg | Thr | Ile | Phe | Phe | Lys | Asp | Asp | Gly |
| | | | | 580 | | | | | 585 | | | | | 590 | | |
| | Asn | Tyr | Lys | Thr | Arg | Ala | Glu | Val | Lys | Phe | Glu | Gly | Asp | Thr | Leu | Val |
| | | | 595 | | | | | 600 | | | | | 605 | | | |
| 40 | Asn | | Ile | Glu | Leu | Lys | | Ile | Asp | Phe | Lys | | Asp | Gly | Asn | Ile |
| | T | 610 | 77. | T | • | a 1 | 615 | | _ | | _ | 620 | | | | |
| | 625 | GIY | HIS | ràs | Leu | 630 | Tyr | Asn | Tyr | Asn | | His | Asn | Val | Tyr | |
| | | Δla | Agn | Lazg | Gln | | Aen | Gly | Tla | Lvc | 635 | Λαn | Dho | Tara | Tlo | 640 |
| 45 | | ALU | тор | Ly S | 645 | Lys | A511 | Gly | 116 | 650 | vaı | ASII | PHE | цуs | 655 | Arg |
| _ | His | Asn | Ile | Glu | Asp | Glv | Ser | Val | Gln | | Ala | Asp | His | Tvr | | Gln |
| | | | | 660 | - | - | | | 665 | | | | | 670 | | |
| | Asn | Thr | Pro | Ile | Gly | Asp | Gly | Pro | Val | Leu | Leu | Pro | Asp | Asn | His | Tyr |
| | | | 675 | | | | | 680 | | | | | 685 | | | |
| 50 | Leu | | Thr | Gln | Ser | Ala | | Ser | Lys | Asp | Pro | Asn | Glu | Lys | Arg | Asp |
| | | 690 | | _ | _ | | 695 | | | _ | | 700 | _ | | | |
| | | Met | val | Leu | Leu | | Phe | Val | Thr | Ala | | Gly | Ile | Thr | Leu | |
| | 705 Met | V ~~~ | G1 | Len | Фъ | 710 | | | | | 715 | | | | | 720 |
| 55 | ec | Asp | GLU | ח∈u | Tyr 725 | пув | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |

160

| | 160 | |
|----|--|-----|
| | (2) INFORMATION FOR SEQ ID NO:72: | |
| 5 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2751 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 10 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | |
| 15 | (A) NAME/KEY: Coding Sequence (B) LOCATION: 12748 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72: | |
| | | |
| 20 | ATG GCT GAC GTT TAC CCG GCC AAC GAC TCC ACG GCG TCT CAG GAC GTG Met Ala Asp Val Tyr Pro Ala Asn Asp Ser Thr Ala Ser Gln Asp Val 1 5 10 15 | 48 |
| 25 | GCC AAC CGC TTC GCC CGC AAA GGG GCG CTG AGG CAG AAG AAC GTG CAT Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His 20 25 30 | 96 |
| | GAG GTG AAA GAC CAC AAA TTC ATC GCC CGC TTC TTC AAG CAA CCC ACC Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr 35 40 45 | 144 |
| 30 | TTC TGC AGC CAC TGC ACC GAC TTC ATC TGG GGG TTT GGG AAA CAA GGC Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gln Gly 50 55 60 | 192 |
| 35 | TTC CAG TGC CAA GTT TGC TGT TTT GTG GTT CAT AAG AGG TGC CAT GAG Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu 70 75 80 | 240 |
| 40 | TTC GTT ACG TTC TCT TGT CCG GGT GCG GAT AAG GGA CCT GAC ACT GAC Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp 85 90 95 | 288 |
| 45 | GAC CCC AGG AGC AAG CAC AAG TTC AAA ATC CAC ACA TAC GGA AGC CCT Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro 100 105 110 | 336 |
| | ACC TTC TGT GAT CAC TGT GGG TCC CTG CTC TAT GGA CTT ATC CAC CAA Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln 115 120 125 | 384 |
| 50 | GGG ATG AAA TGT GAC ACC TGC GAC ATG AAT GTT CAC AAC CAG TGT GTG Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val 130 135 140 | 432 |

160

480

160

ATC AAT GAC CCT AGC CTC TGC GGA ATG GAT CAC ACA GAG AAG AGG GGG Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly

155

| | 999 | * mm | m » m | ama | | 00m | ~~~ | ama | | a. m | | | ama | | ama | | |
|----|-----|------------|------------|------------|-------------------|-------|------------|------------|------------|------|------|------------|------------|------------|-----|-----|------|
| | | | | | AAG Lys 165 | | | | | | | | | | | | 528 |
| 5 | | | | | | | | | | | | | | | | | |
| | GTA | CGA | GAT | GCA | AAA | AAT | CTA | ATC | CCT | ATG | GAT | CCA | AAT | GGG | CTT | TCG | 576 |
| | Val | Arg | Asp | Ala 180 | Lys | Asn | Leu | Ile | Pro 185 | Met | Asp | Pro | Asn | Gly 190 | Leu | Ser | |
| 10 | GAT | CCT | TAT | GTG | AAG | CTG | AAA | CTA | ATC | CCT | GAC | CCC | AAG | AAT | GAG | AGC | 624 |
| | Asp | Pro | Tyr 195 | Val | Lys | Leu | Lys | Leu 200 | Ile | Pro | Asp | Pro | Lys 205 | Asn | Glu | Ser | |
| | AAA | CAG | AAA | ACC | AAA | ACC | ATC | CGC | TCC | AAC | CTG | AAT | CCT | CAG | TGG | AAT | 672 |
| 15 | Lys | Gln 210 | Lys | Thr | Lys | Thr | Ile 215 | Arg | Ser | Asn | Leu | Asn 220 | Pro | Gln | Trp | Asn | |
| | GAG | TCC | TTC | ACG | TTC | AAA | TTA | AAA | CCT | TCA | GAC | AAA | GAC | CGG | CGA | CTG | 720 |
| | Glu | Ser | Phe | Thr | Phe | Lys | Leu | Lys | Pro | Ser | Asp | Lys | Asp | Arg | Arg | Leu | |
| 20 | 225 | GM3 | <i>a</i> | . | maa | 230 | | | | | 235 | | | a. a | mma | 240 | 7.50 |
| | | | | | TGG Trp | | | | | | | | | | | | 768 |
| | Ser | vai | GIU | 116 | 245 | Mah | тър | Asp | Arg | 250 | 1111 | Arg | MSII | АБР | 255 | Mec | |
| 25 | | | | | | | | | | | | | | | | | |
| | GGA | TCC | CTT | TCC | TTT | GGT | GTC | TCA | GAG | CTA | ATG | AAG | ATG | CCG | GCC | AGT | 816 |
| | Gly | Ser | Leu | Ser | Phe | Gly | Val | Ser | Glu | Leu | Met | Lys | Met | Pro | Ala | Ser | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| 30 | GGA | TGG | тат | מממ | GCT | CAC | ልልሮ | ממי | GDD | GNG | GGC | GDD | ייימיי | ጥልሮ | ממכ | GTG | 864 |
| - | | | | | Ala | | | | | | | | | | | | 001 |
| | • | - | 275 | • | | | | 280 | | | 2 | | 285 | | | | |
| | | | | | | | | | | | | | | | | | |
| | | _ | | _ | GGA | | | | | | | | | | _ | | 912 |
| 35 | Pro | | Pro | Glu | Gly | Asp | | Glu | Gly | Asn | Met | | Leu | Arg | Gln | Lys | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | TTT | GAG | AAA | GCC | AAG | CTA | GGT | CCT | GTT | GGT | AAC | AAA | GTC | ATC | AGC | CCT | 960 |
| | Phe | Glu | Lys | Ala | Lys | Leu | Gly | Pro | Val | Gly | Asn | Lys | Val | Ile | Ser | Pro | |
| 40 | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | TCA | CAA | GNC | אכא | AAG | ריא א | CCX | TCC | 770 | מממ | CTC | CAC | אכא | CTC | מממ | CTC | 1008 |
| | | | | | Lys | | | | | | | | | | | | 1008 |
| | 001 | | | | 325 | 01 | 110 | 001 | 7.511 | 330 | пси | пор | 9 | vuz | 335 | Dea | |
| 45 | | | | | | | | | | | | | | | | | |
| | ACA | GAC | TTC | AAC | TTC | CTC | ATG | GTG | CTG | GGG | AAG | GGG | AGT | TTT | GGG | AAG | 1056 |
| | Thr | Asp | Phe | | Phe | Leu | Met | Val | | Gly | Lys | Gly | Ser | | Gly | Lys | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| 50 | GTG | ATG | CTT | GCT | GAC | AGG | AAG | GGA | ACG | GAG | GAA | CTG | TAC | GCC | ATC | AAG | 1104 |
| | | | | | Asp | | | | | | | | | | | | |
| | | | 355 | | - | _ | - | 360 | | - | | | 365 | | | - | |
| | | | | | | | | | | | | | | | | | |
| EE | • | | | | GAC | | | | | | | | | | | | 1152 |
| 55 | ile | | гуз | тÀг | Asp | vaı | | тте | GIn | Asp | Asp | _ | val | Glu | Cys | Inr | |
| | | 370 | | | | | 375 | | | | | 380 | | | | | |

| | AT Me | 'G G' | TG G | AG A lu L | AG C | GC G | TG C | TG (| 3CC | СТ | G CI | rg g | AC | AAG | ccc | G CC | 'АТ | тт | CTG | 1200 |
|----|-------------------|-------------------|-------------------|----------------------|------------|----------------|-------------------|-----------------------------|---------------|-------------------|------------------|------------|----------------|------------|---------------------|-------------------|------------|----------|------------|------|
| 5 | 38 | 5 | | | | 3 | 90 | cu , | 41 d | Let | ם נו | u A | sp 95 | Lys | Pro | Pr | O P. | he | Leu 400 | 1200 |
| | AC. Th | A CA | AG C | rg ca eu H: | AC TO | | GC T ys P | TC C | CAG Sln | ACA Thi | 4 GI Va 41 | I A | AC (| CGG Arg | CTG | та Ту | C T | 1e | GTC Val | 1248 |
| 10 | AT0 Met | G GA t Gl | LA TA | AC GI Vr Va 42 | | AC G(in G) | GC GC | EG G | AT sp | CTI Leu 425 | Me | G TA | AC (| CAC His | ATT Ile | CAG Gl: | n Gl | A.n | GTC Val | 1296 |
| 15 | | • | 43 | | | | O GI | 4 | 40 | vaı | Phe | е Ту | m A | la | Ala 445 | Glı | ıIl | e | Ser | 1344 |
| 20 | | 45 | ō | G TT u Ph | | | 45 | 5 5 | ув . | Arg | GI | , 11 | e I 4 | le ' 60 | Tyr | Arg | As | р 1 | Leu | 1392 |
| 25 | 465 | | | C AA' n Ası | - , | 47 | 0 | u As | 5 11 ; | ser | GIU | 47 | у Н. 5 | is 1 | Ile | ГÀЗ | Ile | e 1 4 | Ala 180 | 1440 |
| | - | | - | 3 ATO | 485 | , <u>.</u> ., | 3 616 | , UI | . S P | чес | Met 490 | Ası | o G | ly V | /al | Thr | Th: | · A | lrg | 1488 |
| 30 | ACC Thr | TTC | TGC Cys | GGA Gly 500 | | Pro | GAC Asp | С ТА Э Ту | T I | TT le | GCC Ala | CCA | A GA | AG A | le | ATC Ile 510 | GCT Ala | T | AC Yr | 1536 |
| 35 | CAG Gln | CCG Pro | TAC Tyr 515 | GGG | AAG Lys | TCT Ser | GTA Val | GA As _] 52 | b 1 | GG 'rp ' | TGG Trp | GCG Ala | TA Ty | r G | GT (ly \ 25 | GTG Val | CTG Leu | r C | TG eu | 1584 |
| 40 | TAC Tyr | GAG Glu 530 | ATG Met | CTA Leu | GCC Ala | GGG Gly | CAG Gln 535 | CC. | r c | CG ' | TTT Phe | GAT Asp | GG G1 54 | у G | AA C lu <i>A</i> | AT Asp | GAA Glu | Gi A: | AT sp | 1632 |
| 45 | GAA Glu 545 | | | | - | 550 | Mec | GIL | ı H. | ıs A | Asn | Val 555 | Se | r Tj | /r P | ro . | Lys | Se 56 | er 50 | 1680 |
| | TTG | | - | | 565 | , | SCI | 116 | . C } | /s I 5 | ys 70 | GГÀ | Let | ı M∈ | t T | hr i | Lys 575 | Gl | .n | 1728 |
| 50 | CCT (| | - | 580 | | | Cys | сту | 58 | 15 | ıu (| GLY | Glu | ı Ar | g A: 5: | sp V 90 | /al | Ar | g | 1776 |
| 55 | GAG C | CAT lis | GCC Ala 595 | TTC Phe | TTC Phe | AGG Arg | AGG Arg | ATC Ile 600 | GA As | CT PT | GG (| GAG Glu | AAA Lys | CT Le | u G | AG A | AAC Asn | AG Ar | a G | 1824 |

| 5 | | | | CCC Pro | | | | | | | 1872 |
|----|--|--|--|-------------------|--|---|---|---|---|---|------|
| J | | | | CGA Arg | | | | | | | 1920 |
| 10 | | | | ATA Ile | | | | | | | 1968 |
| 15 | | | | GTG Val | | | _ | | _ | | 2016 |
| 20 | | | | GAA Glu 680 | | | | _ | _ | | 2064 |
| 25 | | | | GAT Asp | | _ | | _ | | _ | 2112 |
| | | | | GCA Ala | | | | | | | 2160 |
| 30 | | | | CTA Leu | | | | | | _ | 2208 |
| 35 | | | | CAA Gln | | | | | | | 2256 |
| 40 | | | | AAG Lys 760 | | | | | | | 2304 |
| 45 | | | | AAA Lys | | | | | | | 2352 |
| | | | | GAT Asp | | | | | | | 2400 |
| 50 | | | | GAT Asp | | | | _ | | | 2448 |
| 55 | | | | AAT Asn | | | | | | | 2496 |

| 5 | AAG Lys | AAT Asn | GGC Gly 835 | ATC Ile | AAA Lys | GTT Val | AAC Asn | TTC Phe 840 | ьуз | ATT | AG Ar | A C | is A | AAC . Asn : | ATT Ile | AAA Lys | GAT Asp | 2544 |
|----|-------------------|-------------------|------------------------------------|----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|----------|--------------|----------------|--------------------|-------------------|-------------------|------|
| | GGA Gly | AGC Ser 850 | GTT Val | CAA Gln | TTA Leu | GCA Ala | GAC Asp 855 | CAT His | TAT | CAA Gln | CA Gli | n As | AT A sn T | CT (| CCA Pro | ATT Ile | GGC Gly | 2592 |
| 10 | GAT Asp 865 | GGC Gly | CCT Pro | GTC Val | CTT Leu | TTA Leu 870 | CCA Pro | GAC Asp | AAC Asn | CAT His | TAC Tyr 875 | r Le | rg T eu S | CC F er 1 | CG hr | CAA Gln | TCT Ser 880 | 2640 |
| 15 | GCC Ala | CTT Leu | TCC . Ser : | 4 - | GAT Asp 885 | CCC Pro | AAC Asn | GAA Glu | AAG Lys | AGA Arg 890 | GAT Asp | CA Hi | AC A' | TG A et I | le : | CTT Leu 895 | CTT Leu | 2688 |
| 20 | GAG Glu | TTT Phe | GTA Z Val : | ACA Thr 900 | GCT Ala | GCT Ala | GGG Gly | ATT Ile | ACA Thr 905 | CAT His | GGC Gly | AT Me | G GA | sp G | AA (lu I 10 | CTA Leu | TAC Tyr | 2736 |
| 25 | AAA Lys | CCT (Pro (| CAG (Gln (| BAG ' | ΓΑΑ | | | | | | | | | | | | | 2751 |
| | | | | | | | | | | | | | | | | | | |
| 30 | | (| (2) SEQ A) L B) T C) S | UENC ENGT YPE: | E CH H: 9 | 916 a .no a | TERI | STIC | cs: | NO : 7 | 3: | | | | | | | |
| 35 | | (ii | D) To) MO: FRAG | OPOL LECU | OGY: LE T | lin YPE: | ear pro | tein | 1 | | | | | | | | | |
| | | (xi |) SE(| QUEN | CE D | ESCR: | IPTI | ON: | SEO | א תד | ī 0 . 7 | ٠. | | | | | | |
| 40 | Met A | la As | sp Va | al Ty | yr Pi | ro A | la A | sn A | sp S | er T | hr i | Ala | | | | | | |
| | Ala A | sn Aı | rg Ph | ie Al | la A | rg Ly | /s G | ly A | la L | eu A | rg (| Gln | Lys | Ası | ı Va |) 1 н | is | |
| | Glu V | | | | | | | | | | | | | | | | | |
| 45 | Phe C | 35 | ; 17.2 | _ ~ | | | 4(|) | -u A | -y P | ne i | rne | ьуs 45 | Glr | ı Pr | O T | hr | |
| | Phe Cy |) | T HI | s cy | 's Tr | ır As 55 | p Ph | ne I | le T | rp G | ly I | Phe | Gly | Lys | Gl | n G | ly | |
| | Phe G | ln Cy | s Gl | n Va | .1 Cy | s Cy | s Ph | e Va | al Va | al H | is I | ys | Arg | Cys | Hi | s G] | lu | |
| 50 | Phe Va | al Th | r Ph | e Se | r Cy | s Pr | o Gl | y Al | la As | 79 p Ly | 5 ys G | ilv | Pro | Asn | Th | 80 r 70 |) :D | |
| | Asp Pr | o Ar | g Se: | 85 r Ly | s Hi | s Ly | s Ph | e I.v. | 90 75 T1 |) | ia m | 'h∽ | т | p | 95 | - A: | ٠,٢ | |
| | Thr Ph | ie Cv | 100 | 0 0 # 1 | e ^- | | - •• | 10 | 5 | - ni | ro I | 111, | ıyr | 110 | Se: | r Pr | 0 | |
| 55 | Thr Ph | 11. | 5 | - ui | ь су | s GI | y Se 12 | r Le O | u Le | u Ty | r G | ly | Leu 125 | Ile | His | s Gl | n | |
| | Gly Me | t Ly | s Cys | s As _l | p Th | r Cy | s As | р Ме | t As | n Va | l H | is . | Asn | Gln | Суя | s Va | 1 | |

| | | | | | | | | | | ,00 | | | | | | |
|----|-----------|------|------|----------|------------|----------|----------|------------|-----|------------|-----------|-------------|------|-------|-------------|-------|
| | | 130 | | | | | 135 | | | | | 140 | | | | |
| | Ile | Asn | Asp | Pro | Ser | Leu | Cys | Gly | Met | Asp | His | Thr | Glu | Lys | Arg | Gly |
| | 145 | | _ | | | 150 | - | _ | | • | 155 | | | _ | - | 160 |
| | Arg | Ile | Tyr | Leu | Lys | Ala | Glu | Val | Thr | qaA | Glu | Lys | Leu | His | Val | Thr |
| 5 | | | | | 165 | | | | | 170 | | | | | 175 | |
| | Val | Arg | Asp | Ala | Lys | Asn | Leu | Ile | Pro | Met | Asp | Pro | Asn | Gly | Leu | Ser |
| | | | | 180 | | | | | 185 | | | | | 190 | | |
| | qaA | Pro | Tyr | Val | Lys | Leu | Lys | Leu | Ile | Pro | Asp | ${\tt Pro}$ | Lys | Asn | Glu | Ser |
| | | | 195 | | | | | 200 | | | | | 205 | | | |
| 10 | Lys | Gln | Lys | Thr | Lys | Thr | Ile | Arg | Ser | Asn | Leu | Asn | Pro | Gln | Trp | Asn |
| | | 210 | | | | | 215 | | | | | 220 | | | | |
| | Glu | Ser | Phe | Thr | Phe | _ | Leu | Lys | Pro | Ser | _ | Lys | Asp | Arg | Arg | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| | Ser | Val | Glu | Ile | - | Asp | Trp | Asp | Arg | | Thr | Arg | Asn | Asp | | Met |
| 15 | | _ | _ | _ | 245 | | - | | | 250 | | _ | | _ | 255 | _ |
| | GIA | Ser | Leu | | Phe | Gly | Val | ser | | Leu | Met | Lys | Met | Pro | Ala | ser |
| | 01 | m | m | 260 | 27- | 774 - | 7 | a 1 | 265 | a 1 | 01 | 01 | m | 270 | 7 | 17- 1 |
| | GIY | Trp | _ | ьуѕ | AIA | HIS | Asn | | GIU | GIU | GIY | GIU | _ | Tyr | Asn | vai |
| 20 | n | 710 | 275 | C1 | C1., | 700 | C1 | 280 | C1 | 7.00 | Mot | C1 | 285 | X ~~~ | Cln. | Tira |
| 20 | PIO | 290 | PIO | Giu | GIY | Asp | 295 | GIU | Gry | ASII | Mec | 300 | Leu | Arg | GIII | ьуѕ |
| | Dhe | | Lva | - ר ה | Lare | Len | | Dro | V=1 | Glv | λen | _ | V= l | Ile | Ser | Pro |
| | 305 | Giu | Буз | AIG | БуБ | 310 | Gry | FIO | vai | Gry | 315 | Llys | vai | 116 | JCI | 320 |
| | | Glu | Asp | Ara | Lvs | | Pro | Ser | Agn | Asn | | Asp | Ara | Val | Lvs | |
| 25 | | | | | 325 | | | | | 330 | | | 5 | | 335 | |
| | Thr | αsA | Phe | Asn | | Leu | Met | Val | Leu | | Lys | Gly | Ser | Phe | | Lys |
| | | | | 340 | | | | | 345 | • | - | • | | 350 | • | • |
| | Val | Met | Leu | Ala | Asp | Arg | Lys | Gly | Thr | Glu | Glu | Leu | Tyr | Ala | Ile | Lys |
| | | | 355 | | _ | _ | _ | 360 | | | | | 365 | | | |
| 30 | Ile | Leu | Lys | Lys | Asp | Val | Val | Ile | Gln | Asp | Asp | Asp | Val | Glu | Cys | Thr |
| | | 370 | | | | | 375 | | | | | 380 | | | | |
| | Met | Val | Glu | Lys | Arg | Val | Leu | Ala | Leu | Leu | Asp | Lys | Pro | Pro | Phe | Leu |
| | 385 | | | | | 390 | | | | | 395 | | | | | 400 |
| | Thr | Gln | Leu | His | | Cys | Phe | Gln | Thr | | Asp | Arg | Leu | Tyr | | Val |
| 35 | | | _ | _ | 405 | | • | | _ | 410 | | | | | 415 | |
| | Met | Glu | Tyr | | Asn | Gly | Gly | Asp | | Met | Tyr. | His | Ile | Gln | Gln | Val |
| | ~1 | • | n1 | 420 | a 3 | D | a1- | -1- | 425 | -1 | _ | | | 430 | -1 - | |
| | GIY | гÀг | | гув | GIU | Pro | GIn | | vaı | Pne | Tyr | Ala | | Glu | me | ser |
| 40 | T7.0 | C114 | 435 | Dho | Dho | Ι | 1114.0 | 440 | 7~~ | a1 | T10 | т1. | 445 | Arg | N am | T ON |
| 40 | 116 | 450 | Leu | Pne | Pne | ren | 455 | rys | Arg | GIÀ | 116 | 460 | Tyr | Arg | Asp | Leu |
| | Lave | | λen | Agn | Val | Met | | Δen | Ser | Glu | Glv | | Tle | Lys | Tle | Δla |
| | 465 | пец | Hall | ven | vai | 470 | пси | VOII | Ser | GIU | 475 | 1115 | 116 | цуз | 110 | 480 |
| | | Phe | Glv | Met | Cvs | | Glu | His | Met | Met | | Glv | Val | Thr | Thr | |
| 45 | ··· | | 027 | | 485 | -7- | | | | 490 | | - 1 | | | 495 | 5 |
| | Thr | Phe | Cys | Glv | | Pro | asp | Tyr | Ile | | Pro | Glu | Ile | Ile | | Tyr |
| | | | 1 | 500 | | | - | • | 505 | | | | | 510 | | |
| | Gln | Pro | Tyr | Gly | Lys | Ser | Val | Asp | Trp | Trp | Ala | Tyr | Gly | Val | Leu | Leu |
| | | | 515 | _ | _ | | | 520 | _ | _ | | - | 525 | | | |
| 50 | Tyr | Glu | Met | Leu | Ala | Gly | Gln | Pro | Pro | Phe | Asp | Gly | Glu | Asp | Glu | Asp |
| | | 530 | | | | | 535 | | | | | 540 | | | | |
| | | Leu | Phe | Gln | Ser | Ile | Met | Glu | His | Asn | Val | Ser | Tyr | Pro | Lys | |
| | 545 | | | | | 550 | | | | | 555 | | | | | 560 |
| | Leu | Ser | Lys | Glu | | Val | Ser | Ile | Cys | | Gly | Leu | Met | Thr | | Gln |
| 55 | Δ | | | | 565 | | _ | | _ | 570 | | | | | 575 | |
| | Pro | Ala | гуѕ | Arg | Leu | GIA | Cys | GLY | Pro | Glu | GIY | GLu | Arg | Asp | val | arg |
| | | | | | | | | | | | | | | | | |

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580
                                     585
       Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
                          600
      Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
  5
                              615
                                                620
      Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
                         630
                                             635
      Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                     645
                                         650
      Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
 10
                                      665
      Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
                                 680
                                                    685
      Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
15
                            695
                                                 700
      Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
                       710
                                          715
      Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
                                        730
      Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
20
                  740
                                    745
      Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
                         760
      Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
25
                             775
                                                 780
      Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
                         790
                                             795
      Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
                     805
                                         810
      Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
30
                 820
                                    825
      Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
                                840
      Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
35
                             855
                                               860
      Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
                      870
                                           875
      Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
                    885
                                        890
     Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
40
                 900
                                                        910
     Lys Pro Gln Glu
            915
45
              (2) INFORMATION FOR SEQ ID NO:74:
           (i) SEQUENCE CHARACTERISTICS:
             (A) LENGTH: 2157 base pairs
             (B) TYPE: nucleic acid
50
             (C) STRANDEDNESS: single
             (D) TOPOLOGY: linear
           (ii) MOLECULE TYPE: cDNA
```

(A) NAME/KEY: Coding Sequence

(ix) FEATURE:

167

(B) LOCATION: 1...2154(D) OTHER INFORMATION:

(xi) SEOUENCE DESCRIPTION: SEO ID NO:74:

| 5 | | () | ci) S | EQUI | ENCE | DESC | CRIP | CION: | SEC |) ID | NO: | 74: | | | | | |
|----|---------|----------|-------|-------|------------|-------------|------|-------|---------|----------|----------|-------|--------|--------------|---------|---------|-----|
| | ATG | TCG | TCC | ATC | TTG | CCA | TTC | ACG | CCG | CCA | GTT | GTG | AAG | AGA | CTG | CTG | 48 |
| | Met | Ser | Ser | Ile | Leu | Pro | Phe | Thr | Pro | Pro | Val | Val | Lys | Arg | Leu | Leu | |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| | | | | | | | | | | | | | | | | | |
| 10 | | | | | TCA | | | | | | | | | | | | 96 |
| | Gly | Trp | Lys | - | Ser | Ala | Gly | Gly | | Gly | Gly | Ala | Gly | - | Gly | Glu | |
| | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | CNG | ידי אי א | ccc | CNG | GAA | G N N | አአር | TCC | יייטייי | CAC | *** | CCA | GTG | מממ | א כיייי | CTC | 144 |
| 15 | | | | _ | Glu | _ | | | | | | | | | | | 144 |
| | | | 35 | | | | _, _ | 40 | 0,0 | | _,_ | | 45 | / - | | 200 | |
| | | | | | | | | | | | | | | | | | |
| | GTG | AAG | AAG | CTA | AAG | AAA | ACA | GGA | CGA | TTA | GAT | GAG | CTT | GAG | AAA | GCC | 192 |
| | Val | Lys | Lys | Leu | Lys | Lys | Thr | Gly | Arg | Leu | qaA | Glu | Leu | Glu | Lys | Ala | |
| 20 | | 50 | | | | | 55 | | | | | 60 | | | | | |
| | አጥሮ | אככ | A CT | Chh | AAC | TOT | እ አጥ | A CIT | *** | TOT | Cmm | N.C.C | מידי מ | CCN | n.c.c | א כייני | 240 |
| | | | | | Asn | | | | | | | | | | | | 240 |
| | 65 | | | | | 70 | | | _,, | -ys | 75 | | | | | 80 | |
| 25 | | | | | | | | | | | | | | | | | |
| | TGC | TCT | GAA | ATT | TGG | GGA | CTG | AGT | ACA | CCA | AAT | ACG | ATA | GAT | CAG | TGG | 288 |
| | Cys | Ser | Glu | Ile | Trp | Gly | Leu | Ser | Thr | Pro | Asn | Thr | Ile | Asp | Gln | Trp | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| 30 | 0 B III | 202 | 202 | 000 | Omm. | m | 300 | mma | mam | <i>-</i> | <i>-</i> | 3.00 | 3.00 | mam | amm | anm. | 226 |
| 30 | | | | | CTT Leu | | | | | | | | | | | | 336 |
| | p | | | 100 | 200 | - 1 - | | | 105 | Ozu | 0111 | | 9 | 110 | 200 | 7102 | |
| | | | | | | | | | | | | | | | | | |
| | GGT | CGT | CTC | CAG | GTA | TCC | CAT | CGA | AAA | GGA | TTG | CCA | CAT | GTT | ATA | TAT | 384 |
| 35 | Gly | Arg | Leu | Gln | Val | Ser | His | Arg | Lys | Gly | Leu | Pro | His | Val | Ile | Tyr | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | maa | 007 | mma | maa | ~~~ | maa | 00m | G 3 m | omm | ~~~ | 3 cm | ~~~ | ~~~ | C.D.D | ama | 220 | 433 |
| | | | | | CGC Arg | | | | | | | | | | | | 432 |
| 40 | Cys | 130 | Deu | 115 | Arg | 11p | 135 | rop | Deu | 1112 | 361 | 140 | 1115 | Giu | пси | БуЗ | |
| | | | | | | | | | | | | | | | | | |
| | GCA | ATT | GAA | AAC | TGC | GAA | TAT | GCT | TTT | AAT | CTT | AAA | AAG | GAT | GAA | GTA | 480 |
| | Ala | Ile | Glu | Asn | Cys | Glu | Tyr | Ala | Phe | Asn | Leu | Lys | Lys | Asp | Glu | Val | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| 45 | mam | am. | | | m> c | a. a | | | | | | | | | | oom | |
| | | _ | | | TAC | | | _ | | | | | | _ | | | 528 |
| | Суз | vai | ASII | FIO | Tyr 165 | nis | ıyı | GIII | Arg | 170 | GIU | THIL | PIO | vai | 175 | PIO | |
| | | | | | | | | | | | | | | | | | |
| 50 | CCA | GTA | TTA | GTG | CCC | CGA | CAC | ACC | GAG | ATC | CTA | ACA | GAA | CTT | CCG | CCT | 576 |
| | Pro | Val | Leu | Val | Pro | Arg | His | Thr | Glu | Ile | Leu | Thr | Glu | Leu | Pro | Pro | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| | ama | ~~~ | ~~~ | m > m | 3.00 | a. - | mee | * c | 005 | | | | | mer e | | 001 | |
| 55 | | | | | ACT Thr | | | | | | _ | | | | | | 624 |
| 55 | Jeu | νοħ | 195 | - y - | 1111 | 1113 | SET | 200 | F10 | GIU | voii | TILL | 205 | FIIC | FIO | N10 | |
| | | | | | | | | | | | | | | | | | |

| 5 | GGA ATT GAG CCA CAG AGT AAT TAT ATT CCA GAA ACG CCA CCT CCT GGA Gly Ile Glu Pro Gln Ser Asn Tyr Ile Pro Glu Thr Pro Pro Pro Gly 210 215 220 | 672 |
|----|---|------|
| | TAT ATC AGT GAA GAT GGA GAA ACA AGT GAC CAA CAG TTG AAT CAA AGT Tyr Ile Ser Glu Asp Gly Glu Thr Ser Asp Gln Gln Leu Asn Gln Ser 230 235 240 | 720 |
| 10 | ATG GAC ACA GGC TCT CCA GCA GAA CTA TCT CCT ACT ACT CTT TCC CCT Met Asp Thr Gly Ser Pro Ala Glu Leu Ser Pro Thr Thr Leu Ser Pro 245 250 255 | 768 |
| 15 | GTT AAT CAT AGC TTG GAT TTA CAG CCA GTT ACT TAC TCA GAA CCT GCA Val Asn His Ser Leu Asp Leu Gln Pro Val Thr Tyr Ser Glu Pro Ala 260 265 270 | 816 |
| 20 | TTT TGG TGT TCA ATA GCA TAT TAT GAA TTA AAT CAG AGG GTT GGA GAA Phe Trp Cys Ser Ile Ala Tyr Tyr Glu Leu Asn Gln Arg Val Gly Glu 275 280 285 | 864 |
| 25 | ACC TTC CAT GCA TCA CAG CCC TCA CTC ACT GTA GAT GGC TTT ACA GAC Thr Phe His Ala Ser Gln Pro Ser Leu Thr Val Asp Gly Phe Thr Asp 290 295 300 | 912 |
| | CCA TCA AAT TCA GAG AGG TTC TGC TTA GGT TTA CTC TCC AAT GTT AAC Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly Leu Leu Ser Asn Val Asn 305 310 315 | 960 |
| 30 | CGA AAT GCC ACG GTA GAA ATG ACA AGA AGG CAT ATA GGA AGA GGA GTG Arg Asn Ala Thr Val Glu Met Thr Arg Arg His Ile Gly Arg Gly Val 325 330 335 | 1008 |
| 35 | CGC TTA TAC TAC ATA GGT GGG GAA GTT TTT GCT GAG TGC CTA AGT GAT Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe Ala Glu Cys Leu Ser Asp 340 345 350 | 1056 |
| 40 | AGT GCA ATC TTT GTG CAG AGC CCC AAT TGT AAT CAG AGA TAT GGC TGG Ser Ala Ile Phe Val Gln Ser Pro Asn Cys Asn Gln Arg Tyr Gly Trp 355 360 365 | 1104 |
| 45 | 370 375 Pro Pro Gly Cys Asn Leu Lys Ile | 1152 |
| | 385 390 Leu Leu Ala Gln Ser Val Asn Gln 395 400 | 1200 |
| 50 | GGT TTT GAA GCC GTC TAT CAG CTA ACT AGA ATG TGC ACC ATA AGA ATG Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg Met Cys Thr Ile Arg Met 405 410 415 | 1248 |
| 55 | AGT TTT GTG AAA GGG TGG GGA GCA GAA TAC CGA AGG CAG ACG GTA ACA Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr Arg Arg Gln Thr Val Thr 420 425 430 | 296 |
| | | 100 |

| | | | | | | | | | | | | | | | CAG | | 1344 |
|----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-------------------|-----|------|
| 5 | Ser | Thr | Pro 435 | Cys | Trp | Ile | Glu | Leu 440 | His | Leu | Asn | Gly | Pro 445 | Leu | Gln | Trp | |
| | | | | _ | | | | | | | | | | | TGC Cys | | 1392 |
| 10 | | | | | | | | | | | | | | | ACC Thr | | 1440 |
| 15 | _ | | | _ | _ | _ | | | | | | | | | CTG Leu 495 | | 1488 |
| 20 | | | | | | | | | | | | | | | GGC Gly | | 1536 |
| 25 | _ | | _ | | | | | | | | | | | | ATC Ile | | 1584 |
| | | | | | | | | | | | | | | | ACC Thr | | 1632 |
| 30 | | | | | | | | | | | | | | | AAG Lys | | 1680 |
| 35 | | | | | | | | | | | | | | | GAG Glu 575 | | 1728 |
| 40 | | _ | | | | | | | | | | | | | GAG Glu | | 1776 |
| 45 | | | | | | | | | | | | | | | GGC Gly | | 1824 |
| 45 | | | | | | | | | | | | | | | TAC Tyr | | 1872 |
| 50 | | | | | | | | | | | | | | | AAC Asn | | 1920 |
| 55 | | | | | | | | | | | | | | | AGC Ser 655 | | 1968 |

| 5 | | | | | 66 | 0 | | 7. | GIII | GI. | n As | sn 1 55 | hr I | Pro | Ile | Gl | y A 6 | sp G 70 | ly | CCC Pro | 2016 |
|----|------------------|------|-------------------|-------------------|-------------------|-------------------------|----------------------|----------------------|-------------------|------------|----------|--------------|--------------|--------------------|-------------------|------------|-----------|------------------|----------|------------|------|
| | V: | al I | Jeu Jeu | Leu 675 | Pr | C G | AC A sp A | AC sn | CAC His | TA: | L Le | rg A eu S | GC A er 1 | CC hr | CAG Gln | TC Se: | r A. | CC C la L | TG eu | AGC Ser | 2064 |
| 10 | A <i>l</i> Ly | AA C | SAC Isp S90 | CCC Pro | AA As | C GI | AG A | , 5 | CGC Arg 695 | GAT Asp | CA Hi | CA' | rg g et V | al l | CTG Leu 700 | CT(Let | G GA | AG T | TC he | GTG Val | 2112 |
| 15 | AC Th 70 | | CC la | GCC Ala | GG(| G AT | C 1, | CT (nr 1 10 | CTC Leu | GGC Gly | AT Me | G GA | sp G | AG (lu I 15 | TG eu | ТАС Туг | AA Ly | GT) 's | A.A | | 2157 |
| 20 | | | (i) | SE | QUE | ifor Ence | CHA | RAC | TER | IST | ICS | | 75 | : | | | | | | | |
| 25 | | | , | (A) (B) (C) | LEN TYP STR | GTH E: AND OLO | : 71 amin EDNE | .8 a .0 a .SS: | min cid si | o a | cid | 5 | | | | | | | | | |
| 30 | | | (V) | FR | AGM | CULI ENT | TYP | E: | inte | erna | al | | | | | | | | | | |
| | Met | | | | | | | | | | | | | :75 | | | | | | | |
| 22 | | | | | | | | | | | | | | | | | | Lei 15 Gly | | | |
| 35 | | | | | | | | | | | | | | | | | | Ser | | | |
| | | | | | | | | Th | ır G | | | | | | | | | Lys | | | |
| 40 | | | | | | | | | | | | | Va: | | | | | Ser | | | |
| | | | | | | | Gly | | | | | | | | | | | Gln | | r p | |
| 45 | | | | | | | | | | | | Glu | | | | | | 95 Leu | | | |
| | Gly | | | | | | | | | rg] | Lys | | | | | s ' | | | | | |
| 50 | Cys | | | | | | | | | | | | | | | s (| | | | | |
| 50 | Ala 145 | | | | | | | | | | | | | Ly | з Ьу | | | | | | |
| | Суз | Val | As | n P | ro ' | Tyr 165 | His | Ту | r Gl | n A | Arg | Val 170 | Glu | Thi | Pr | 7 0 | /al | Leu | 16 Pr | 0 | |
| 55 | Pro | | | | | | | | | | lu | Ile | | | | | | | | | |
| | Leu | Asp | As | рΤ | r' | Fhr | His | Ser | : 11 | e F | ro | Glu | Asn | Thr | As | u E | .90 he | Pro | Al | a | |

| | | | | | | | | | | 171 | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | | | 195 | | | | | 200 | | | | | 205 | | | |
| | Gly | Ile 210 | Glu | Pro | Gln | Ser | Asn 215 | Tyr | Ile | Pro | Glu | Thr 220 | Pro | Pro | Pro | Gly |
| 5 | Tyr 225 | Ile | Ser | Glu | Asp | Gly 230 | | Thr | Ser | Asp | Gln 235 | | Leu | Asn | Gln | Ser 240 |
| | | Asp | Thr | Gly | Ser 245 | | Ala | Glu | Leu | Ser 250 | | Thr | Thr | Leu | Ser 255 | |
| | Val | Asn | His | Ser 260 | _ | Asp | Leu | Gln | Pro 265 | | Thr | Tyr | Ser | Glu 270 | | Ala |
| 10 | Phe | Trp | Cys 275 | | Ile | Ala | Tyr | Tyr 280 | | Leu | Asn | Gln | Arg 285 | | Gly | Glu |
| | Thr | Phe 290 | His | Ala | Ser | Gln | Pro 295 | Ser | Leu | Thr | Val | Asp 300 | Gly | Phe | Thr | Asp |
| 15 | Pro 305 | Ser | Asn | Ser | Glu | Arg 310 | Phe | Сув | Leu | Gly | Leu 315 | Leu | Ser | Asn | Val | Asn 320 |
| | Arg | Asn | Ala | Thr | Val 325 | Glu | Met | Thr | Arg | Arg 330 | His | Ile | Gly | Arg | Gly 335 | Val |
| | Arg | Leu | Tyr | Tyr 340 | Ile | Gly | Gly | Glu | Val 345 | Phe | Ala | Glu | Cys | Leu 350 | Ser | Asp |
| 20 | Ser | Ala | Ile 355 | Phe | Val | Gln | Ser | Pro 360 | Asn | Cys | Asn | Gln | Arg 365 | Tyr | Gly | Trp |
| | | Pro 370 | | | | _ | 375 | | | | - | 380 | | | - | |
| 25 | 385 | Asn | | | | 390 | | | | | 395 | | | | | 400 |
| | | Phe | | | 405 | | | | | 410 | | | | | 415 | |
| | | Phe | | 420 | | | | | 425 | | | | | 430 | | |
| 30 | | Thr | 435 | _ | _ | | | 440 | | | | _ | 445 | | | _ |
| | | Asp 450 | | | | | 455 | | | | | 460 | | | | |
| 35 | 465 | Met | | _ | | 470 | _ | | _ | _ | 475 | | | | | 480 |
| | | Ser | | | 485 | | | | | 490 | | | | | 495 | |
| 40 | | Leu | | 500 | | | | | 505 | _ | | | | 510 | | |
| 40 | | Glu | 515 | | | | _ | 520 | _ | | | | 525 | | | _ |
| | | Thr | | | | | 535 | | | | | 540 | | | | |
| 45 | 545 | Tyr | | | | 550 | | | | - | 555 | _ | | | _ | 560 |
| | | Asp Ile | | | 565 | | | | | 570 | | | | | 575 | |
| 50 | | Phe | | 580 | | | | | 585 | | - | | _ | 590 | | |
| | | Phe | 595 | | | | | 600 | | | | | 605 | | | |
| | | 610 Asn | | | | | 615 | | | | | 620 | | | | |
| 55 | 625 | | | | | 630 | | | | | 635 | -1- | | -1- | | 640 |
| | Ile | Lys | Val | Asn | Phe | | Ile | Arg | His | Asn | | Glu | Asp | Gly | Ser | |

172 650 Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro 665 Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser 5 680 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 695 700 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 710 10 (2) INFORMATION FOR SEQ ID NO:76: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2397 base pairs 15 (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA 20 (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2394 (D) OTHER INFORMATION: 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76: ATG GAC AAT ATG TCT ATT ACG AAT ACA CCA ACA AGT AAT GAT GCC TGT Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys 48 30 10 CTG AGC ATT GTG CAT AGT TTG ATG TGC CAT AGA CAA GGT GGA GAG AGT Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser 96 25 35 GAA ACA TTT GCA AAA AGA GCA ATT GAA AGT TTG GTA AAG AAG CTG AAG Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys 144 40 GAG AAA AAA GAT GAA TTG GAT TCT TTA ATA ACA GCT ATA ACT ACA AAT 40 Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn 192 GGA GCT CAT CCT AGT AAA TGT GTT ACC ATA CAG AGA ACA TTG GAT GGG Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly 45 240 AGG CTT CAG GTG GCT GGT CGG AAA GGA TTT CCT CAT GTG ATC TAT GCC Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala 288

172

384

CGT CTC TGG AGG TGG CCT GAT CTT CAC AAA AAT GAA CTA AAA CAT GTT Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val 105

AAA TAT TGT CAG TAT GCG TTT GAC TTA AAA TGT GAT AGT GTC TGT GTG

90

50

| | | | | | | | | | | 173 | | | | | | | | |
|----|-----|-----|------------|-----|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|------|--------|
| | Lys | Tyr | Cys 115 | Gln | Tyr | Ala | Phe | Asp 120 | Leu | Lys | Cys | Asp | Ser 125 | Val | Cys | Val | | |
| 5 | | | | | TAC Tyr | | | | | | | | | | | | 432 | |
| 10 | | | | | CAG Gln | | | | | | | | | _ | | | 480 | |
| 15 | | | | | GAC Asp 165 | | | | | | | | | | _ | _ | 528 | |
| 15 | | | | | ACC Thr | | | | | | | | | _ | | | 576 | |
| 20 | | | | | ACC Thr | | | | | | | | | | | | 624 | |
| 25 | | | | | AAC Asn | | | | | | | | | | | _ | 672 | |
| 30 | | | | | CTG Leu | | | | | | | | | | | _ | 720 | |
| | | | | | CAG Gln 245 | | | | | | | | | | | | 768 | |
| 35 | | | | | CAT His | | | | | | | | | _ | | | 816 | ; |
| 40 | | | | | ACA Thr | | | | | | | | | | _ | | 864 | |
| 45 | | | | | CCT Pro | | | | | | | | | | | _ | 912 | |
| 50 | | | | | GCA Ala | | | | | | | | | | | | 960 | 1 |
| | | | | | TCC Ser 325 | | | | | | | | | | | | 1008 | 3 |
| 55 | GAG | ACA | TTT | AAG | GTT | CCT | TCA | AGC | TGC | CCT | ATT | GTT | ACT | GTT | GAT | GGA | 1056 | ; 1 |

| | | | | | | | | | | | 174 | | | | | | | | | |
|----|------------|--------------------|---------------------|------------|--------------------|--------------|-------|----------------------|--------------------|------------|------------|------------|--------------|--------------------|------------|--------------|-----------|------------|------|-----|
| | Gl | u T | hr P | he L | ys V 40 | al P | ro S | er S | er (| | | Ile | e Va | 1 T | | al 1 50 | \sp | Gly | | |
| 5 | ТА Ту | C G | | AC Cosp Po | CT T | CT G er G | GA G | TY A | AT C sp A 60 | GC rg | TTT Phe | TG1 Cys | Г ТТ з Le | G G(u G] 36 | ST C | | TC eu | TCC Ser | 11 | 04 |
| 10 | AA As: | T G7 n Va 37 | TC C al H: 70 | AC A(| GG AG | CA G | Lu A | CC A' la II 75 | rr g le G | AG . | AGA Arg | GCA Ala | A AG | g Le | G C | AC A is I | TA le | GGC Gly | 11 | 52 |
| 15 | 385 | 5 | | | AG TI | 39 | 90 | ∖а гу | rs G. | ry (| 31u | Gly 395 | ' Ası | o Va | 1 T1 | p V | al | Arg 400 | 12 | 00 |
| 20 | _ | | | | C CA P Hi 40 | 5 | a va | I Ph | ie va | 4 | 110 | Ser | Туг | ту | r Le | u As | sp 15 | Arg | 124 | 18 |
| 20 | | | | 42 | | u 11 | o gi | y As | р А1 42 | .a v :5 | 'a I | His | Lys | Ile | Э Ту 43 | r Pr O | О. | Ser | 129 | 6 |
| 25 | | • | 43 | 5 | G GT | | c As | 44 | u Ar | g G | ın ı | Cys | His | Arc 445 | g Gl: | n Me | t (| Gln | 134 | 4 |
| 30 | | 450 |) | | r ACT | . Ale | 455 | i Ala | a Al | аА | la A | Ala | Ala 460 | Gln | Ala | a Al | a I | Ala | 139 | 2 |
| 35 | 465 | | 2 | | C ATO | 470 |) Gly | PIC |) GI | y Se | er V | /al 175 | Gly | Gly | Ile | Al: | a F 4 | ro 80 | 1440 | 0 |
| 40 | | | | | TCA Ser 485 | 71.0 | , TI | нта | GI | 49 | le G | ily ' | Val | Asp | Asp | Let 495 | ı A | rg | 1488 | 3 |
| 40 | CGC | | -1- | 500 | Deu | nr 9 | Mec | ser | 505 | va | t L | ys (| Gly | Trp | Gly 510 | Pro | A | sp | 1536 | i |
| 45 | TAC Tyr | | 515 | | 501 | 116 | Lys | 520 | Thr | Pr | o C; | ys 1 | ſrp | Ile 525 | Glu | Ile | H: | is | 1584 | |
| 50 | | 530 | | | 204 | 0111 | 535 | ren | Asp | G1 | u Va | al L 5 | eu 1 | His | Thr | Met | Pı | co | 1632 | |
| 55 | ATT (Ile A | | | | 0.111 | 550 | пеп | Asp | Trp | Asj | 9 Pr 55 | CO P | ro V | Val | Ala | Thr | Ме 5 6 | t 0 | 1680 | |
| | GTG A | AGC . | AAG | GGC | GAG | GAG | CTG | TTC | ACC | GGG | 3 GT | rg g | TG (| ccc . | ATC | CTG | GT | rc | 1728 | 174 |

| | | | | | | | | | | 175 | | | | | | | |
|----|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----------|
| | Val | Ser | Lys | Gly | Glu 565 | Glu | Leu | Phe | Thr | Gly 570 | Val | Val | Pro | Ile | Leu 575 | Val | |
| 5 | | | | | GAC Asp | | | | | | | | | | | | 1776 |
| 10 | _ | _ | _ | | GCC Ala | | | _ | | | | | | | | | 1824 |
| 15 | | | | | CTG Leu | | | | | | | | | | | | 1872 |
| 13 | | | | | CAG Gln | | | | | | | | | | | | 1920 |
| 20 | | | | | AAG Lys 645 | | | | | | | | | | | | 1968 |
| 25 | | | | | AAG Lys | | | | | | | | | | | | 2016 |
| 30 | | | | | GAC Asp | | | | | | | | | | | | 2064 |
| | | | | | GAC Asp | | | | | | | | | | | | 2112 |
| 35 | | | | | AAC Asn | | | | | | | | | | | | 2160 |
| 40 | | | | | TTC Phe 725 | | | | | | | | | | | | 2208 |
| 45 | | | | | CAC His | | | | | | | | | | | | 2256 |
| 50 | | | | | GAC Asp | | | | | | | | | | | | 2304 |
| 55 | | | | | GAG Glu | | | | | | | | | | | _ | 2352 |
| 55 | ACC | GCC | GCC | GGG | ATC | ACT | стс | GGC | ATG | GAC | GAG | CTG | TAC | AAG | TAA | | 2397 1 |

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785 790 795

5 (2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 798 amino acids
- (B) TYPE: amino acid

10

15

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys

20 Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser

Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys
35 40

Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn

50
55
60

Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly
65 70 75 80

Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala

Lys Tyr Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val 115 120 125

Asn Pro Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser

35 130 135 140

Gly Leu Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp

145 150 150

Glu Tyr Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly

165

170

40 His Ser Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr
180 185 180

Glu Thr Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala

Thr Ser Thr 200 205

Thr Ser Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln

215
220

50 Pro Ala Thr Tyr His His Asn Ser Thr Thr Thr Thr Thr Gly Ser Arg

Thr Ala Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu 275 280 285

Gln His His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val

295

295

300

His Asn Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro

| | | | | | | | | | | 177 | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| | Glu | Tyr | Trp | Cys | Ser 325 | Ile | Ala | Tyr | Phe | Glu 330 | Met | Asp | Val | Gln | Val 335 | Gly |
| 5 | Glu | Thr | Phe | Lys 340 | Val | Pro | Ser | Ser | Cys 345 | Pro | Ile | Val | Thr | Val 350 | Asp | Gly |
| | Tyr | Val | Asp 355 | Pro | Ser | Gly | Gly | Asp 360 | Arg | Phe | Cys | Leu | Gly 365 | Gln | Leu | Ser |
| | Asn | Val 370 | His | Arg | Thr | Glu | Ala 375 | Ile | Glu | Arg | Ala | Arg 380 | Leu | His | Ile | Gly |
| 10 | Lys 385 | Gly | Val | Gln | Leu | Glu 390 | Суз | Lys | Gly | Glu | Gly 395 | Asp | Val | Trp | Val | Arg 400 |
| | Cys | Leu | Ser | Asp | His 405 | Ala | Val | Phe | Val | Gln 410 | Ser | Tyr | Tyr | Leu | Asp 415 | Arg |
| 15 | Glu | Ala | Gly | Arg 420 | Ala | Pro | Gly | Asp | Ala 425 | Val | His | Lys | Ile | Tyr 430 | Pro | Ser |
| | Ala | Tyr | Ile 435 | Lys | Val | Phe | Asp | Leu 440 | Arg | Gln | Cys | His | Arg 445 | Gln | Met | Gln |
| | Gln | Gln 450 | Ala | Ala | Thr | Ala | Gln 455 | Ala | Ala | Ala | Ala | Ala 460 | Gln | Ala | Ala | Ala |
| 20 | Val 465 | Ala | Gly | Asn | Ile | Pro 470 | Gly | Pro | Gly | Ser | Val 475 | Gly | Gly | Ile | Ala | Pro 480 |
| | Ala | Ile | Ser | Leu | Ser 485 | Ala | Ala | Ala | Gly | Ile 490 | Gly | Val | Asp | Asp | Leu 495 | Arg |
| 25 | Arg | Leu | Cys | Ile 500 | Leu | Arg | Met | Ser | Phe 505 | Val | ГÀЕ | Gly | Trp | Gly 510 | Pro | Asp |
| | Tyr | Pro | Arg 515 | Gln | Ser | Ile | Lys | Glu 520 | Thr | Pro | Cys | Trp | Ile 525 | Glu | Ile | His |
| | Leu | His 530 | Arg | Ala | Leu | Gln | Leu 535 | Leu | Asp | Glu | Val | Leu 540 | His | Thr | Met | Pro |
| 30 | 545 | | _ | | Gln | 550 | | _ | _ | _ | 555 | | | | | 560 |
| | | | | | Glu 565 | | | | | 570 | | | | | 575 | |
| 35 | | | | 580 | Asp | | | _ | 585 | _ | | | | 590 | | |
| | | | 595 | _ | Ala | | - | 600 | - | | | | 605 | | | |
| 40 | | 610 | | | Leu | | 615 | | _ | | | 620 | | | | |
| 40 | 625 | | | | Gln | 630 | | | | | 635 | | | | | 640 |
| | | _ | | | Lys 645 | | | | | 650 | _ | _ | | | 655 | _ |
| 45 | | | | 660 | Lys | _ | - | - | 665 | - | - | | _ | 670 | | |
| | | | 675 | _ | Asp | | | 680 | | _ | | | 685 | | _ | |
| 50 | | 690 | | | Asp | _ | 695 | | | _ | | 700 | | | _ | |
| 50 | 705 | | | | Asn | 710 | - | | | | 715 | _ | | - | | 720 |
| | | | | | Phe 725 | | | | | 730 | | | | | 735 | |
| 55 | | | | 740 | His | | | | 745 | | | | | 750 | | |
| | val | ⊾eu | ьeu | Pro | Asp | Asn | Hls | Tyr | Leu | ser | Inr | GIn | ser | Ala | Leu | ser |

| | 755 760 765 Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 770 775 | | | | | | | | | | | | |
|----|--|------------|--|--|--|--|--|--|--|--|--|--|--|
| | 770 775 780 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 | | | | | | | | | | | | |
| 5 | 785 790 795 | | | | | | | | | | | | |
| | (2) INFORMATION FOR SEQ ID NO:78: | | | | | | | | | | | | |
| 10 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3138 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | | | | | | | | | | | | |
| 15 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | | | | | | | | | | | | |
| 20 | (A) NAME/KEY: Coding Sequence (B) LOCATION: 13135 (D) OTHER INFORMATION: | | | | | | | | | | | | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78: | | | | | | | | | | | | |
| 25 | ATG GCG GGC TGG ATC CAG GCC CAG CAG CTG CAG GGA GAC GCG CTG CGC Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg 1 5 10 15 | 48 | | | | | | | | | | | |
| 30 | CAG ATG CAG GTG CTG TAC GGC CAG CAC TTC CCC ATC GAG GTC CGG CAC Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His | 96 | | | | | | | | | | | |
| | 25 30 | | | | | | | | | | | | |
| 35 | TAC TTG GCC CAG TGG ATT GAG AGC CAG CCA TGG GAT GCC ATT GAC TTG Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu 35 40 45 | 144 | | | | | | | | | | | |
| | GAC AAT CCC CAG GAC AGA GCC CAA GCC ACC CAG CTC CTG GAG GGC CTG Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu 50 60 | 192 | | | | | | | | | | | |
| 40 | GTG CAG GAG CTG CAG AAG AAG GCG GAG CAC CAG GTG GGG GAA GAT GGG Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 65 70 75 80 | 240 | | | | | | | | | | | |
| 45 | TTT TTA CTG AAG ATC AAG CTG GGG CAC TAC GCC ACG CAG CTC CAG AAA Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys 85 90 95 | 288 | | | | | | | | | | | |
| 50 | ACA TAT GAC CGC TGC CCC CTG GAG CTG GTC CGC TGC ATC CGG CAC ATT Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile 100 105 110 | 336 | | | | | | | | | | | |
| 55 | CTG TAC AAT GAA CAG AGG CTG GTC CGA GAA GCC AAC AAT TGC AGC TCT Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 115 120 125 | 384 | | | | | | | | | | | |
| | CCG GCT GGG ATC CTG GTT GAC GCC ATG TCC CAG AAG CAC CTT CAG ATC | 432 178 | | | | | | | | | | | |

| | | | | | | | | | | 179 | | | | | | | |
|----|-----|------------|-----|-----|-------------------|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------|
| | Pro | Ala 130 | Gly | Ile | Leu | Val | Asp 135 | Ala | Met | Ser | Gln | Lys 140 | His | Leu | Gln | Ile | |
| 5 | | | | | GAG Glu | | | | | | | | | | | | 480 |
| 10 | | | | | CTG Leu 165 | | | | | | | | | | | | 528 |
| 15 | | | | | AGG Arg | | | | | | | | | | | | 576 |
| | | | | | CGT Arg | | | | | | | | | | | _ | 624 |
| 20 | | | | | GCC Ala | | | | | | | | | | | | 672 |
| 25 | | | | | CTG Leu | | | | | _ | | | | _ | | | 720 |
| 30 | | | | | ACC Thr 245 | | | | | | | | | | | | 768 |
| 35 | | | | | CTG Leu | | | | | | | | | | | | 816 |
| 00 | | | | | TCC Ser | | | | | | | | | | | _ | 864 |
| 40 | | | | | ATC Ile | | | | | | | | | | | | 912 |
| 45 | | | | | GTG Val | | | | | | | | | | | | 960 |
| 50 | | | | | TCA Ser 325 | | | | | | | | | | | | 1008 |
| 55 | | | | | GTC Val | | | | | | | | | | | | 1056 |
| 00 | CGC | CTG | CTG | GTG | GGC | GGG | AAG | CTG | AAC | GTG | CAC | ATG | AAT | CCC | CCC | CAG | 1104 |

| | A T | _ | | | | | | 180 | | | | | | |
|------|---------------------------|-----------------------|-----------------------|-------------------------|-----------------------|--------------------|-----------------------|-----------------------|-----------------------|-----------------------|------------------------|----------------------|-------------------------|-------------|
| | | | | | | 3 | 80 | | | | 365 | | ro Gln | |
| 5 | GTG A Val L 3 | AG GC ys Al 70 | C ACC | ATC . | | GT G er G 75 | AG <i>CE</i> lu Gl | AG CA | G GCC n Ala | AAG Lys 380 | TCT C | TG C | IT AAA eu Lys | 1152 |
| 10 | AAT G. Asn G. 385 | AG AA lu As | C ACC | 5 - | AAC G Asn G 390 | AG TO | GC AG /s Se | T GG | r GAG y Glu 395 | ATC (| CTG A Leu A | AC AA sn As | AC TGC sn Cys 400 | 1200 |
| 15 | TGC G | TG AT al Me | G GAG t Glu | TAC (Tyr H 405 | CAC CA His Gl | AA GC ln Al | CC AC | G GGC r Gly 410 | Thr | CTC I | AGT G | CC CA la Hi 41 | s Phe | 1248 |
| | AGG AA Arg As | AC ATO | G TCA E Ser 420 | CTG A | AG AC | G AT | C AA0 e Ly: | s Arg | GCT Ala | GAC C | CGG CO Arg Ai | g Gl | T GCA y Ala | 1296 |
| 20 | GAG TO Glu Se | C GTC r Val 435 | ACA Thr | GAG G Glu G | AG AA lu Ly | G TT s Ph | e ini | A GTC Val | CTG Leu | Phe G | AG TO llu Se | T CAG | G TTC | 1344 |
| 25 | AGT GT Ser Va 45 | T GGC l Gly O | AGC Ser | AAT G | AG CT lu Le 45 | u va. | G TTC l Phe | CAG Gln | Val | AAG A Lys T 460 | CT CT | G TC(| C CTA | 1392 |
| 30 . | CCT GTO Pro Val 465 | G GTT l Val | GTC . Val | ATC GT Ile Va | | C GGC | C AGC / Ser | CAG Gln | GAC (Asp 1475 | CAC A | AT GC | C ACG a Thr | GCT Ala 480 | 1440 |
| 35 | ACT GTO | G CTG Leu | | GAC AA Asp As 185 | T GCC | TTT Phe | GCT Ala | GAG Glu 490 | CCG (| GGC AG | GG GTO | G CCA Pro 495 | TTT Phe | 1488 |
| | GCC GTG Ala Val | CCT Pro | GAC A Asp I 500 | AAA GT ys Va | G CTG l Leu | TGG Trp | CCG Pro 505 | CAG Gln | CTG T Leu C | GT GA | AG GCC u Ala 510 | Leu | AAC Asn | 1536 |
| 40 | ATG AAA Met Lys | TTC Phe 515 | AAG G Lys A | CC GA | A GTG u Val | CAG Gln 520 | AGC Ser | AAC (Asn i | CGG G Arg G | GC CT ly Le 52 | u Thr | AAG Lys | GAG Glu | 1584 |
| 45 | AAC CTC Asn Leu 530 | GTG Val | TTC C Phe L | TG GCO eu Ala | G CAG Gln 535 | AAA Lys | CTG Leu | TTC / | Asn A | AC AG sn Se: | C AGC r Ser | AGC Ser | CAC His | 1632 |
| 50 | CTG GAG Leu Glu 545 | GAC Asp | TAC A | GT GGC er Gly 550 | neu | TCC Ser | GTG Val | ser 1 | GG TG Trp Se | CC CAC | G TTC n Phe | Asn | AGG Arg 560 | 1680 |
| 55 | GAG AAC Glu Asn | TTG (| CCG GC Pro Gl | GC TGG ly Trp 55 | AAC Asn | TAC Tyr | Inr 1 | TTC T Phe T | GG CF | AG TGO In Trp | TTT Phe | GAC Asp | GGG Gly | 1728 |
| | GTG ATG | GAG (| etg ti | G AAG | AAG | CAC | CAC A | AAG C | CC CA | C TGG | З ААТ | GAT (| GGG | 1776 180 |

| | | | | | | | | | | 181 | | | | | | | |
|----|------------|------------|-------------------|------------|-------------------|------------|------------|-------------------|---------------------|------------|------------|------------|-------------------|------------|------------|------------|------|
| | Val | Met | Glu | Val 580 | Leu | Lys | Lys | His | His 5 8 5 | Lys | Pro | His | Trp | Asn 590 | Asp | Gly | |
| 5 | | | | | TTT Phe | | | | | | | | | | | | 1824 |
| 10 | | | | | GGG Gly | | | | | | | | | | | | 1872 |
| 4- | | | | | ATC Ile | | | | | | | | | | | | 1920 |
| 15 | | | | | CCA Pro 645 | | | | | | | | | | | | 1968 |
| 20 | | | | | GGG Gly | | | | | | | | | | | | 2016 |
| 25 | | | | | GAG Glu | | | | | | | | | | | | 2064 |
| 30 | | | | | GGA Gly | | | | | | | | | | | | 2112 |
| | | | | | GCA Ala | | | | | | | | | | | | 2160 |
| 35 | | | | | CCC Pro 725 | | | | | | | | | | | | 2208 |
| 40 | | | | | AAC Asn | | | | | | | | | | | | 2256 |
| 45 | GAC Asp | CTG Leu | GAT Asp 755 | GAG Glu | ACC Thr | ATG Met | GAT Asp | GTG Val 760 | GCC Ala | AGG Arg | CAC His | GTG Val | GAG Glu 765 | GAA Glu | CTC Leu | TTA Leu | 2304 |
| 50 | | | | | GAC Asp | | | | | | | | | | | | 2352 |
| | | | | | GCC Ala | | | | | | | | | | | | 2400 |
| 55 | GAT | CCA | CCG | GTC | GCC | ACC | ATG | GTG | AGC | AAG | GGC | GAG | GAG | CTG | TTC | ACC | 2448 |

| | 182 | |
|----|--|-------------|
| | Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr 805 810 815 | |
| 5 | GGG GTG GTG CCC ATC CTG GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His 820 825 830 | 2496 |
| 10 | AAG TTC AGC GTG TCC GGC GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys 835 840 845 | 2544 |
| 15 | CTG ACC CTG AAG TTC ATC TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp 850 855 860 | 2592 |
| 00 | CCC ACC CTC GTG ACC ACC CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg 865 870 875 880 | 2640 |
| 20 | TAC CCC GAC CAC ATG AAG CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro 885 890 895 | 2688 |
| 25 | GAA GGC TAC GTC CAG GAG CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn 900 905 910 | 2736 |
| 30 | TAC AAG ACC CGC GCC GAG GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn 915 920 925 | 2784 |
| 35 | CGC ATC GAG CTG AAG GGC ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu 930 935 940 | 2832 |
| | GGG CAC AAG CTG GAG TAC AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met 950 955 960 | 2880 |
| 40 | GCC GAC AAG CAG AAG AAC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His 965 970 975 | 2928 |
| 45 | AAC ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn 980 985 990 | 2976 |
| 50 | ACC CCC ATC GGC GAC GGC CCC GTG CTG CCC GAC AAC CAC TAC CTG Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu 995 1000 1005 | 3024 |
| 55 | AGC ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His 1010 1015 1020 | 3072 |
| | ATG GTC CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG | 3120 182 |

183

Met Val Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met 1025 1030 1035 1040

GAC GAG CTG TAC AAG TAA
5 Asp Glu Leu Tyr Lys

3138

(2) INFORMATION FOR SEQ ID NO:79:

10

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1045 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
- 15

50

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
 (v) FRAGMENT TYPE: internal
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg

1 5 10 15

Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 25 30

25 20 25 30

Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu

35 40 Ara Gin 11p 11e Giu Ser Gin Pro 11p Asp Ara 11e Asp Leu

Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Glu Gly Leu
50 55 60

30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly
65 70 75 80
Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys

85 90 95 Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile

35 100 105 110 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 115 120 125

Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile 130 135 140

Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 145 150 155 160

Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr 165 170 175

Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 180 185 190

Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 195 200 205

Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln
210 215 220

Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 225 230 235 240 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys

245 250 255
Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu

55 260 265 270
Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

| | | | | | | | | | | | | | 184 | 1 | | | | | | | | |
|----|-------------------|------------|------------|--------------------|------------|------------|------------|------------|------------|-----------|-------------|-------------------|------------|------------|------------|------------|------------|------------|----------|----------|-----------|------------|
| | | | | 27 | | | | | | 2 | 80 | | | | | | _ | | | | | |
| | A | sn | Arg 290 | g Gl | n G] | ln I | le A | Arg | Arg 295 | A | la | Glu | Hi | s L | eu | Су | s G | 85 ln (| ln | Le | u 1 | Pro |
| | I | le | Pro | Gl | y Pr | o v | al (| Slu | Gli |) 1 M/ | - +- | Lan | ד ה | | 1 | 300 |) | | | | | |
| 5 | 3 | 05 | | | | | 3 | 10 | | | | Leu | WI | a G | 1u | ۷a. | L As | sn A | la | Th | r] | lle |
| | T | hr : | Asp | Ile | e I1 | e s | er A | lla | Let | l Vá | al ' | Thr | Se | r T | hr | Phe | • I] | le I | le | Gl | 3 u I | 320 .vs |
| | G. | ln i | Pro | Pro | Gl | n V | 25 al L | eu | Lys | Tł | ır (| 31n | 33 Th: | 0 r L | ys | Phe | : A] | аА | la | 33 Th | 5 r 1 | 7a 1 |
| 10 | Aı | rg 1 | Leu | Le: | 34 Va | 0 1 G: | ly G | ly | Lvs | Le | : | 345 Asn | Va. | l u | | | | 3 | 50 | - 11 | | aı |
| | Va | al I | Lvs | 355 Ala | i Th | r T | - _ T | 10 | | 36 | 0 | | va. | . п. | 15 | Met | 36 | in P 5 | ro | Pro | o G | ln |
| | | | | Ala | | | | | | | | | | | | | | | | | | |
| 15 | 38 | 511 C | iu | Asn | Th | r Ar | g A | sn (90 | Glu | Су | s S | er | Gl | 7 G | lu : | Ile | Le | u A | sn | Ası | ı C | ys |
| | СУ | s V | 'al | Met | Glı | и ту | r H | is (| 31n | Al | аŢ | hr | Gly | 3 9 Th | 95 1r] | Leu | Se | r A | la | His | 4 P | 00 be |
| | Ar | g A | sn | Met | Sei | 40 Le | u Ly | ys l | ۱rg | Il | e L | vs | 410 |) 1 A I | аĭ | len | λ~. | ~ A- | | 415 | | |
| 20 | Gl | u S | er | Val | 420 The | , GI | n G | | | nl- | 4 | 25 | | , 111 | .a r | rsb | AL | 9 A1 | .g | GIy | ' A. | la |
| | | | | Val 435 | | | | | | | | | | | | | | | | | | |
| | 36 | 4. | 50 | Gly | Ser | As | n Gl | u I 4 | eu 55 | Va: | l P | he | Gln | Va | 1 L | ys 60 | Thi | . Le | u i | Ser | Le | eu |
| 25 | Pro 469 | o Va 5 | al | Val | Val | . 11 | e Va 47 | l H | is | Gly | S | er | Gln | As | рН | is | Asr | ı Al | a ? | Chr | Al | a |
| | | | | Leu | | Ası | As | | | | | | | | | | | | | | | |
| | | | | Pro | | | | | | | | | | | | | | | | | | |
| 30 | Met | : Ly | /s] | Phe 5 15 | 500 Lys | Ala | Gl: | u V | a ì | Gln | 5(|)5 | | 2 | u c | ys | - GIU | 51 | a 1 0 | eu | As | n |
| | Asn | ı Le | : u v | 515 Val | Phe | Leu | וה | | 1 | 520 | _ | -1 1 | | ALC | 3 G. | тÀ | ьеи 525 | Th | r L | ys | G1 | u |
| | ĭ 0 | 53 | 0 | Val | _ | DC U | AI | a G. 5: | 35 | ьys | ьe | eu I | Phe | Ası | 1 A: | sn 10 | Ser | Se | S | er | Hi | s |
| 35 | | | | Asp | | | | | | | | | | | Se | er (| | | | | | |
| | Glu | As | n I | eu | Pro | Gly 565 | Tr | As | n : | Гуr | Th | rp | he | 555 Trp | G] | n : | Гrр | Phe | : A | sp | 560 Gl | D 7 |
| | Val | Ме | t G | lu | Val | Leu | Lys | ь Гу | s ł | lis | Hi | s L | 70 ys | Pro | Ні | s : | ľrp | Asn | 5 A | 75 sp | Glv | , |
| 40 | Ala | Il | e L | eu (| Gly | Phe | Va1 | . As | n I | ys | 58 Gl: | 5 n G | ln. | Ala | ні | e 1 | - \en | 590 | | • | ~ 7 . | |
| | Asn | Ly | 5 s P | 95 ro <i>l</i> | as! | Glv | Thr | · Ph | 6 A T | 00 | Ι | | | | | 6 | 05 | пец | . Lie | ≠u | 116 | • |
| | Glv | 610 | 0 T | ו מו | The w | T1- | | 61 | 5 | ie u | пe | u A | rg . | Pne | Se 62 | r A O | sp | Ser | G. | Lu | Ile | : |
| 45 | Gly 625 | OI, | γ 1 | 16] | .nr | тте | 630 | Tr | рL | ys | Phe | 2 A: | sp : | Ser 635 | Pr | o G | lu | Arg | As | n] | Leu | |
| | Trp | Ası | ı L | eu I | γys | Pro 645 | Phe | Th | r T | hr | Arg | 3 A: | sp I | Phe | Se | r I | le | Arg | S€ | er] | Leu | |
| | Ala | Asp |) A | rg L | eu (| Gly | Asp | Le | u s | er | Туг | : Le | 50 eu] | lle | ту | r V | al | Phe | 65 Pr | 5 O 1 | qa/ | |
| 50 | Arg | Pro | Ly | /s A | sp (| Glu | Val | Phe | ∍ S | er | 665 Lys | ; : Т <u>у</u> | r T | 'yr | Th | r P | ro | 670 Val | Le | u A | la. | |
| | Lys | Ala | Va | al A | sp (| Gly | Tyr | Va: | 6. L L | 80 Ys | Pro | G] | ln I | le | Lys | 6 3 G | 85 ln | Val | V۵ |) r | | |
| | Glu | oy0 Phe | Va | ıl A | sn 1 | Ala | Ser | 695 | 5 | | | | | _ | 700 |) | | 1 | va | | 10 | |
| 55 | Glu 705 Met | 7 e= | <i>-</i> | | | | 710 | AT. | . AS | ıμ, | мла | . G1 | у G 7 | 1y 15 | Ser | S | er i | Ala | Th | r I | yr 20 | |
| | Met . | чар | GΙ | n A | ıa F | ro. | Ser | Pro |) A] | la ' | Val | Су | s P | ro | Glr | ı A. | la 1 | Pro | ту | r A | sn | |
| | | | | | | | | | | | | | | | | | | | | | | |

185

| | | | | | 725 | | | | | 730 | | | | | 735 | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|------------|------------|------------|
| | Met | Tyr | Pro | Gln 740 | Asn | Pro | Asp | His | Val 745 | Leu | Asp | Gln | Asp | Gly 750 | Glu | Ph∈ |
| 5 | Asp | Leu | Asp 755 | Glu | Thr | Met | Asp | Val 760 | Ala | Arg | His | Val | Glu 765 | Glu | Leu | Lev |
| Ū | Arg | | Pro | Met | Asp | Ser | | | Ser | Arg | Leu | | | Pro | Ala | Gly |
| | | 770 Phe | Thr | Ser | Ala | | 775 Gly | Ser | Leu | Ser | | 780 Val | Pro | Arg | Ala | |
| 10 | 785 Asp | Pro | Pro | Val | | 790 Thr | Met | Val | Ser | _ | 795 Gly | Glu | Glu | Leu | | 800 Thr |
| | Gly | Val | Val | | 805 Ile | Leu | Val | Glu | | 810 Asp | Gly | Asp | Val | | 815 Gly | His |
| | Lys | Phe | Ser | 820 Val | Ser | Gly | Glu | | 825 Glu | Gly | Asp | Ala | | 830 Tyr | Gly | Lys |
| 15 | Leu | Thr | 835 Leu | Lys | Phe | Ile | Сув | 840 Thr | Thr | Gly | Lys | Leu | 845 Pro | Val | Pro | Trp |
| | | 850 | Leu | | | | 855 | | | | | 860 | | | | |
| 20 | 865 | | | | | 870 | | | | | 875 | | | | | 880 |
| 20 | | _ | Asp | | 885 | | | | | 890 | | | | | 895 | |
| | | | Tyr | 900 | | | | | 905 | | | | | 910 | | |
| 25 | Tyr | Lys | Thr 915 | Arg | Ala | Glu | Val | Lys 920 | Phe | Glu | Gly | Asp | Thr 925 | Leu | Val | Asn |
| | Arg | Ile 930 | Glu | Leu | Lys | Gly | Ile 935 | qaA | Phe | Lys | Glu | Asp 940 | Gly | Asn | Ile | Leu |
| | Gly 945 | His | Lys | Leu | Glu | Tyr 950 | Asn | Tyr | Asn | Ser | His 955 | Asn | Val | Tyr | Ile | Met 960 |
| 30 | Ala | Asp | Lys | Gln | Lys 965 | Asn | Gly | Ile | Lys | Val 970 | Asn | Phe | Lys | Ile | Arg 975 | His |
| | Asn | Ile | Glu | Asp 980 | Gly | Ser | Val | Gln | Leu 985 | Ala | Asp | His | Tyr | Gln 990 | Gln | Asn |
| 35 | Thr | Pro | Ile 995 | Gly | Asp | Gly | | Val | | Leu | Pro | | Asn 1005 | | Tyr | Leu |
| | | Thr | Gln | Ser | Ala | | - | | Asp | Pro | | | | Arg | Asp | His |
| | | | Leu | Leu | | | | Thr | Ala | | Gly | | Thr | Leu | - | |
| 40 | | Glu | Leu | Tyr | | 1030 | | | | _ | 1035 | | | | - | 1040 |
| | | | | - | 1045 | | | | | | | | | | | |
| | | | (2) | INI | FORM | OITA | I FOR | SE(| Q ID | NO: 8 | 30: | | | | | |
| | | | | | | | | | | | | | | | | |

- 45 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

50

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TGGGATCCTC AGGCCGTGCT GCTGGCCG

(2) INFORMATION FOR SEQ ID NO:81:

185

| 5 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
|----|--|-----|
| 10 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81: GTCTCGAGGG AGCATGGGCA CCTTGCG | |
| 15 | (2) INFORMATION FOR SEQ ID NO:82:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid | 27 |
| 20 | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82: | |
| 25 | TGGGATCCGA GAAGTCTATA TCCCATC | 27 |
| | (2) INFORMATION FOR SEQ ID NO:83: | |
| 30 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 35 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83: | |
| | TGGGATCCTT AGAAGTCTAT ATCCCATC | 28 |
| 40 | (2) INFORMATION FOR SEQ ID NO:84: (i) SEQUENCE CHARACTERISTICS: | 28 |
| 45 | (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84: | |
| 50 | GTCTCGAGCC ATGAACGCCC CCGAGCGG | 28 |
| | (2) INFORMATION FOR SEQ ID NO:85: | |
| 55 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid | |
| | | 186 |

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(C) STRANDEDNESS: single (D) TOPOLOGY: linear 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85: GTGAATTCTC GTCTGATTTC TGGCAGGAGG 30 (2) INFORMATION FOR SEQ ID NO:86: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86: 20 GTGAATTCTT TACGTCTGAT TTCTGGCAGG 3.0 (2) INFORMATION FOR SEO ID NO:87: (i) SEQUENCE CHARACTERISTICS: 25 (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87: GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC 34 35 (2) INFORMATION FOR SEQ ID NO:88: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid 40 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88: 45 31 GTGGATCCAA GGAGCTGATC TGACTCAGCA G (2) INFORMATION FOR SEQ ID NO:89: 50 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid

187

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

| | 188 | |
|----|--|-----|
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89: | |
| | GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG | 32 |
| 5 | (2) INFORMATION FOR SEQ ID NO:90: | |
| | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs | |
| 10 | (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 15 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90: | |
| | CCTCCTAAGC TTATCATGGA CCATTATGAT TC | 32 |
| | (2) INFORMATION FOR SEQ ID NO:91: | |
| 20 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs | |
| | (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| 25 | (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91: | |
| 30 | CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG | 33 |
| | (2) INFORMATION FOR SEQ ID NO:92: | |
| 35 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 45 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 40 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92: | |
| | GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG | 45 |
| 45 | (2) INFORMATION FOR SEQ ID NO:93: | |
| | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 45 base pairs(B) TYPE: nucleic acid | |
| 50 | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93: | |
| 55 | GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTC TTCCC | 45 |
| | | 100 |

| | 189 | |
|-----|--|----|
| | (2) INFORMATION FOR SEQ ID NO:94: | |
| 5 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 10 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:94: | |
| | GGGAAGCTTC CATGAGCGAG ACGGTCATC | 29 |
| 15 | (2) INFORMATION FOR SEQ ID NO:95: | |
| | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| 20 | (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95: | |
| 25 | CCCGGATCCT CAGGGAGAAC CCCGCTTC | 28 |
| | (2) INFORMATION FOR SEQ ID NO:96: | |
| 30 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 35 | | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96: | 30 |
| 40 | GTGAATTCGA CCATGGAGCG GCCCCCGGGG | 30 |
| | (2) INFORMATION FOR SEQ ID NO:97: (i) SEQUENCE CHARACTERISTICS: | |
| | (A) LENGTH: 27 base pairs(B) TYPE: nucleic acid | |
| 45 | (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 50 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:97: | |
| - • | GTGGTACCCA TTCTGTTAAC CAACTCC | 27 |
| | (2) INFORMATION FOR SEQ ID NO:98: | |
| 55 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs | |

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| | | PC1/DK98/00145 |
|-----|--|----------------|
| | 190 | • |
| | (B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 5 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98: | |
| | GTGGTACCTC ATTCTGTTAA CCAACTCC | 28 |
| 10 | (2) INFORMATION FOR SEQ ID NO:99: | 20 |
| 15 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | |
| 20 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:99: | |
| | GTCTCGAGAG ATGCTGTCCC GTGGGTGG | 28 |
| | (2) INFORMATION FOR SEQ ID NO:100: | |
| 25 | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs | |
| 30 | (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:100: | |
| 35 | GTGAATTCGC TTCCTCTTGA GGGAACC | 27 |
| | (2) INFORMATION FOR SEQ ID NO:101: | |
| 40 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 45 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:101: | |
| | GTGAATTCAC TTCCTCTTGA GGGAACC | 27 |
| 50 | (2) INFORMATION FOR SEQ ID NO:102: | |
| | (i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid | |
| 55 | (C) STRANDEDNESS: single | |
| :10 | (D) monor | |

190

(D) TOPOLOGY: linear

. 191

| GTCTCGAGCC ATGGAGAACT TCCAAAAGG (2) INFORMATION FOR SEQ ID NO:103: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (2) INFORMATION FOR SEQ ID NO:103: GTGGATCCCA GAGTCGAAGA TGGGGTAC (2) INFORMATION FOR SEQ ID NO:104: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
|---|-----|
| (2) INFORMATION FOR SEQ ID NO:103: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:103: GTGGATCCCA GAGTCGAAGA TGGGGTAC (2) INFORMATION FOR SEQ ID NO:104: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | 9 |
| (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:103: GTGGATCCCA GAGTCGAAGA TGGGGTAC (2) INFORMATION FOR SEQ ID NO:104: (1) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: (1) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 | |
| GTGGATCCCA GAGTCGAAGA TGGGGTAC (2) INFORMATION FOR SEQ ID NO:104: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| GTGGATCCCA GAGTCGAAGA TGGGGTAC (2) INFORMATION FOR SEQ ID NO:104: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: (3) GTGGATCCTC AGAGTCGAAG ATGGGGTAC (2) INFORMATION FOR SEQ ID NO:105: (3) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (2) INFORMATION FOR SEQ ID NO:104: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single 25 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | 8 |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single 25 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC 29 (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (B) TYPE: nucleic acid (C) STRANDEDNESS: single 25 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC 29 (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (a) LENGTH: 30 base pairs (b) TYPE: nucleic acid (c) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| 30 GTGGATCCTC AGAGTCGAAG ATGGGGTAC (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (a) LENGTH: 30 base pairs (b) TYPE: nucleic acid (c) STRANDEDNESS: single (d) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (2) INFORMATION FOR SEQ ID NO:105: (i) SEQUENCE CHARACTERISTICS: (a) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | 9 |
| (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid 50 (C) STRANDEDNESS: single | |
| (C) STRANDEDNESS: single (D) TOPOLOGY: linear 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid 50 (C) STRANDEDNESS: single | |
| (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: GTGAATTCGG CGATGCCAGA CCCCGCGGCG (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| GTGAATTCGG CGATGCCAGA CCCCGCGGCG 45 (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid 50 (C) STRANDEDNESS: single | |
| (2) INFORMATION FOR SEQ ID NO:106: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid 50 (C) STRANDEDNESS: single | 0 |
| (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| (B) TYPE: nucleic acid (C) STRANDEDNESS: single | |
| - | |
| (D) TOPOLOGY: linear | |
| | |
| (xi) SEQUENCE DESCRIPTION: SEQ ID NO:106: | |
| 55 GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC 32 | .2 |
| GIGGATGGGA GGGTGAGGGT TC | 191 |

| | (2) INFORMATION FOR SEQ ID NO:107: | |
|----|--|------------|
| 5 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 10 | | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:107: | |
| | GTGGATCCTC AGGCACAGGC AGCCTCAGCC TTC | 33 |
| 15 | (2) INFORMATION FOR SEQ ID NO:108: | |
| 20 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2616 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 25 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | |
| | (A) NAME/KEY: Coding Sequence(B) LOCATION: 12613(D) OTHER INFORMATION: | |
| 30 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108: | |
| 35 | ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 10 15 | 48 |
| | GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 | 96 |
| 40 | GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 | 144 |
| 45 | TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60 | 192 |
| 50 | CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80 | 240 |
| 55 | CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95 | 288 |
| | CGC ACC ATC TTC TAG GAC GAC GGC AAC TAG AAG ACC CGC GCC GAG | 336 192 |

. 193

| | | | | | | | | | | 193 | | | | | | | | |
|-----|-----|-----|-----|------------|-------------------|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|----------|
| | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | Asn | Tyr | Lys | Thr | Arg 110 | Ala | Glu | | |
| 5 | | | | | GGC Gly | | | | | | | | | | | | 38 | 14 |
| 10 | | | | | GAG Glu | | | | | | | | | | | | 43 | 12 |
| 15 | | | | | CAC His | | | | | | | | | | | | 4.8 | 10 |
| | | _ | | | AAC Asn 165 | | | | | | | | | | | | 52 | 8 |
| 20 | | | | | GAC Asp | | | | | | | | | | | | 57 | 6 |
| 25 | | | | | CCC Pro | | | | | | | | | | | | 62 | 4 |
| 30 | | | | | AAC Asn | _ | | | | | | | | | | | 67 | 2 |
| 35 | | | | | GGG Gly | | | | | | | | | | | | 72 | 0 |
| 00 | _ | | | | CGA Arg 245 | _ | | | | | | | | | | | 76 | 8 |
| 40 | | | | | CCC Pro | | | | | | | | | | | | 81 | .6 |
| 45 | _ | | | | AAG Lys | | | | | | | | | | | | 86 | 4 |
| 50 | | | | | CGC Arg | | | | | | | | | | | | 91 | .2 |
| 5.E | | | | | CAC His | | | | | | | | | | | | 96 | 0 |
| 55 | TAC | GCC | АТТ | GCC | GGC | GGC | AAA | GCG | CAC | TGT | GGA | CCG | GCA | GAG | CTC | TGC | 100 |) 8 1 |

| ### Ala He Ala Gly Gly bys Ala His Cys Gly Pro Ala Glu Leu Cys 125 330 ### GAG TTC TAC TCC CGC GAC CCC GAC GGG CTC CCC TGC AAC CTG CGC AAG CLU Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys 340 ### CCC TGC AAC CGG CCG TCG GGC CTC GAC CGC GGG GTC TTC GAC CCC CGC TGC AAC CGC CGC GGG GTC TTC GAC CCC CGC GGC CTC CGC GGC CTC GGC CAC CCC GGG GTC TTC GAC CCC CGC AGA ACG CCC GGG GTC TTC GAC CCC CGC GAG CCC CGC AGA CCC CCC | | 194 |
|--|----|--|
| 100 345 345 346 | | 3.35 |
| TGC CTG CGA GAC GCC ATG GTG CGT GAC TAC GTG CGC CAG ACG TGG AAG TGC CTG CGA GAC GCC ATG GTG CGT GAC TAC GTG CGC CAG ACG TGG AAG TGC CTG CAG GAC GCC ATG GTG CGT GAC TAC GTG CGC CAG ACG TGG AAG TGC CYS Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg Gln Thr Trp Lys 370 370 370 370 380 TGC GAG GGC GAG GCC CTG GAG CAG GCC ATC ATC AGC CAG GCC CGC CAG Leu Glu Glu Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln J95 TGC GAG GAG GCC CTG GAG CAG GCC CAC GAG CGC CTG GAC Leu Glu Clys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr 405 GCG CAG AGC AGC CTG ACG CGT GAG GAC GCC CAC GAG CGC ATG CCC Alis Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly 420 GCG CAG ACC GAC GAC GAC GAC GAC GCC GAG CGC AAA CTT TAC TCT GGG His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly 420 GCG CAG ACC GAC GAC GAC AGG TCC CTG AGG CCG CGG AAG GAC GAC GGC Ala Gln Thr Asp Gly Lys Phe Leu Larg Pro Arg Lys Glu Gln Gly 435 ACA TAC GCC CTG TCC CTC ATC TAT GGG AAG ACG GT TAC CAC TAC CTC Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu 450 ATC AGC CAA GAC AAG GGG GGC AAG TAC TGC AGG GGC ACC AAG 11e Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys 450 ATC AGC CAA GAC AAG GGG GGC AAG TAC TGC CAC GAG GAC ACC AAG 11e Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys 475 ATC AGC CAC AGC CTC GCA CAG GAG TAC TCC CAAC AGC ACC AAG 11e Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys 475 ATC AGC CAC AGC CTC GCA CAG GAG TAC TCC CAAC AGC AGC AGC AGC AGC ACC AAG GGC CTC ATC TAC TGC CTC AAG GAG GCC CAC CAC AGC 11e Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys 485 ATC AGC CAC GGG GCC AGC CTG GCC CAC CCC ACC ACC ACC AGC AGC AGC AGC AGC AGC AGC AGC CTC ACC TAC CTC ACC CAC CCC ACC ACC AGC Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser 500 TG GC CTC ATC TAC TGC CTC AAG AGC AGC CTC CAC CCC ACC CCC ACC ACC AGC CCC CAC CCC ACC CCC ACC CCC ACC CCC ACC ACC ACC AGC AGC AGC AGC AGC AGC | ŧ | 340 345 350 |
| 15 | 10 | 355 360 365 365 |
| 385 390 395 396 397 398 398 399 395 396 397 398 398 398 399 397 398 398 | 15 | 370 375 191 Val Arg Gln Thr Trp Lys |
| 405 410 410 410 415 410 415 416 417 415 417 415 417 415 417 417 | 20 | 385 390 395 400 |
| 420 425 426 427 428 428 428 428 429 420 425 430 430 430 430 430 430 430 43 | 20 | 405 410 Arg Met Pro Trp Tyr |
| ACA TAC GCC CTG TCC CTC ATC TAT GGG AAG ACG GTG TAC CAC TAC CTC THr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu 455 ATC AGC CAA GAC AAG GCG GGC AAG TAC TCC CAG GGC AAG GGC AAG AGG ACG AAG ACG AGG ATG ATG CTC ATC TCC GAG GGC ACC AAG AGG ACG AAG ACG CTC ATC CTC ATC TCC GAG GGC ACC AAG ACG ACG ATG ACG CTC ATC ACG ATC ACG ACG ACG ACG ACG ACG ACG ACG ACG AC | 25 | 420 425 Arg Lys Leu Tyr Ser Gly |
| 35 ATC AGC CAA GAC AAG GCG GGC AAG TAC TGC ATT CCC GAG GGC ACC AAG 1440 ATG AGC CAA GAC AAG GCG GGC AAG TAC TGC ATT CCC GAG GGC ACC AAG 1440 ATG AGC CAA GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC 1488 ATT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC 1488 ABF ABP Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Ala Asp 490 AGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGC AGC AGC AGC AGC GIV Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser 510 AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG 1584 ASN Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr 525 TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC TCC ACG GIV Tyr 530 ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA CCG CGG CCG ATG 1680 ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA CCG CGG CCG ATG 1680 | 30 | 435 440 Arg Lys Glu Gln Gly |
| 465 | 35 | 450 455 460 |
| 40 TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp 495 GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGC AGC GAGC G | | 470 475 470 475 480 |
| GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGT GCC AGC 1536 Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser 510 AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG 1584 Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC TCA GAT GGA TAC 1632 Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr ACC CCT GAG CCA GCA CCC ATA ACG TCC CCA GAC AAA CCC CGG CCG ATG 1680 | 40 | TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG CTG AAG GCG GAC 1488 Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp 485 490 495 |
| AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG 1584 Solvent Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC TCA GAT GGA TAC Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr ACC CCT GAG CCA GCA CCA CCA ACC CTC AAA CCG CGG CCG ATG 1680 | 45 | GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC AGC AGT GCC AGC Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser 500 505 |
| 530 535 540 ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA CCG CGG CCG ATG 1680 | 50 | AAC GCC TCA GGG GCT GCT CCC ACA CTC CCA GCC CAC CCA TCC ACG Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr 515 520 525 |
| | 55 | 530 535 540 Ser Asp Gly Tyr |
| | | |

| | | | | | | | | | | 195 | | | | | | | |
|----|------------|-----|-----|-----|-------------------|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|------|
| | Thr 545 | Pro | Glu | Pro | Ala | Arg 550 | Ile | Thr | Ser | Pro | Asp 555 | Lys | Pro | Arg | Pro | Met 560 | |
| 5 | | | | | AGC Ser 565 | | | | | | | | | | | | 1728 |
| 10 | | | | | AAG Lys | | | | | | | | | | | | 1776 |
| 15 | | | _ | | GGC Gly | | | | | | | | | | | | 1824 |
| | | | | | AAG Lys | | | | | | | | | | | | 1872 |
| 20 | | | | | AAG Lys | | | | | | | | | | | | 1920 |
| 25 | | | | | CTG Leu 645 | | | | | | | | | | | | 1968 |
| 30 | | _ | _ | | GCC Ala | | | | | | | | | | | | 2016 |
| 35 | | | | | TTC Phe | | | | | | | | | | | | 2064 |
| | | | | | CTG Leu | | | | | | | | | | | | 2112 |
| 40 | | | | | TTT Phe | | | | | | | | | | | | 2160 |
| 45 | | | | | CAC His 725 | | | | | | | | | | | | 2208 |
| 50 | | | | | GAC Asp | | | | | | | | | | | | 2256 |
| 55 | | | | | TGG Trp | | | | | | | | | | | | 2304 |
| - | TCC | AGC | CGC | AGC | GAT | GTC | TGG | AGC | TAT | GGG | GTC | ACC | ATG | TGG | GAG | GCC | 2352 |

| | | | | | | | | | | | | | 96 | | | | | | | | |
|----|----------------|------------|-------------------|------------|--------------|-------------|------------|-----------------------|-------------------|--------------|------------|----------|------------|------------|-------------------|-------------------|------------|----------|----------|------------|------|
| | S | er | Ser 770 | Ar | g Se | er A | Asp | Val | Trp 775 | Se: | г ту | r G | ly | Val | Th: | Met | Tr | рG | lu | Ala | |
| 5 | 7 | 85 | | - , . | . 0. | .y C | , 111 | 790 | PIO | ту: | с гъ | s L | ys | Met 795 | Lys | Gly | Pro | o G | lu | 800 | 2400 |
| 10 | | | | | - 11 | 8 | 05 | GIII | GIY | гу | Ar | g M 8 | et 10 | Glu | Cys | CCA Pro | Pro | 6] 8] | lu 15 | Сув | 2448 |
| 15 | | | | | 82 | 0 | 7 ~ | AIA | Dea | Met | 82! | r A: | sp (| Cys | Trp | ATC Ile | Tyr 830 | Ly | 's | Trp | 2496 |
| | | | <u>F</u> - | 835 | 11, | JA | ъÞ | rne | теп | 840 | Val | L G. | lu (| Sln | Arg | ATG Met 845 | Arg | Al | а | Сув | 2544 |
| 20 | ТА | C 1 r 1 | TAC Tyr 150 | AGC Ser | CTO | G GC | CC i | JCI | AAG Lys 855 | GTG Val | GAA Glu | A GG | G C y F | ro | CCA Pro 860 | GGC Gly | AGC Ser | AC Th | A (| CAG Gln | 2592 |
| 25 | AA Ly 86 | s A | CT la | GAG Glu | GCT Ala | GC Al | a (| TGT Cys 370 | GCC Ala | TGA | | | | | | | | | | | 2616 |
| 30 | | | (i |) SE | QUE | NCE | СН | 'ION 'ARA(71 a | TER | ISTI | CS: | МО | :10 | 9: | | | | | | | |
| 35 | | | | (B) (C) | TYP. STR. | E: a | ami EDN | no a ESS: lin | cid sin | | | | | | | | | | | | |
| | | | (ii) |) M FR | OLE(AGMI | CULI ENT | TY: | YPE: PE: | pro inte | otei erna | n 1 | | | | | | | | | | |
| 40 | | | | | | | | ESCR | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | al E | | | | | |
| 45 | | | | | | | | | | | | | | | | er v | al : | Ser | | | |
| | | | | | | | | | | | | | | | | eu L | ys I | | | | |
| 50 | | | | | | | | | | | | | | | | 5 eu V | | | | | |
| | | | | | | | | | | | | | | | | sp H | | | | | |
| | Arg | | | | | | | | | | | | | | | yr V | | | | | |
| 55 | Val | | | | | | | | | | | | | | | | | | | | |
| | | | | | | _ | | | | v | <i>1</i> | 7011 | wτί | 4 T.I | e G. | tu L | eu L | ys | G1 | У | |

| | | | 115 | | | | | 120 | | | | | 125 | | | |
|------|-------|-------------|-------------|------|-----------|-------|-------|------------|-----------|----------|-------------|-------|-----------|----------|------|-------------|
| | Ile | Asp | Phe | Lys | Glu | Asp | Gly | Asn | Ile | Leu | Gly | His | Lys | Leu | Glu | Tyr |
| | | 130 | | - | | | 135 | | | | <u>.</u> | 140 | _ | | | _ |
| | Asn | Tyr | Asn | Ser | His | Asn | Val | Tyr | Ile | Met | Ala | Asp | Lys | Gln | Lys | Asn |
| 5 | 145 | - 2 - | | | | 150 | | | | | 155 | | | | | 160 |
| • | | Tle | Lys | Va 1 | Δen | | Luc | Tle | Ara | Hie | | 716 | Glu | Acn | Gly | |
| | GIY | 116 | цуз | Val | | FIIC | шуз | 116 | Arg | | ASII | 116 | Giu | Asp | _ | Ser |
| | | ~ 3 | - | | 165 | | | ~ 1 | 01 | 170 | | | -7- | | 175 | ~ 1 |
| | vai | GIN | Leu | | Asp | MIS | Tyr | GIU | | ASI | Thr | Pro | TIE | _ | Asp | GIY |
| 4.0 | | _ | | 180 | _ | _ | | • | 185 | | _ | | | 190 | | _0 |
| 10 | Pro | Val | Leu | Leu | Pro | Asp | Asn | | Tyr | Leu | Ser | Thr | | Ser | Ala | Leu |
| | | | 195 | | | | | 200 | | | | | 205 | | | |
| | Ser | Lys | Asp | Pro | Asn | Glu | Lys | Arg | Asp | His | Met | Val | Leu | Leu | Glu | Phe |
| | | 210 | | | | | 215 | | | | | 220 | | | | |
| | Val | Thr | Ala | Ala | Gly | Ile | Thr | Leu | Gly | Met | Asp | Glu | Leu | Tyr | Lys | Ser |
| 15 | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| | Gly | Leu | Arg | Ser | Arg | Ala | Gln | Ala | Ser | Asn | Ser | Ala | Met | Pro | Asp | Pro |
| | - | | _ | | 245 | | | | | 250 | | | | | 255 | |
| | Ala | Ala | His | Leu | Pro | Phe | Phe | Tvr | Glv | Ser | Ile | Ser | Ara | Ala | Glu | Ala |
| | | | | 260 | | | | - | 265 | | | - | | 270 | | |
| 20 | Glu | Glu | His | | Lvg | Len | ΔΊа | Glv | | Δla | Asn | Glv | T.e.11 | | Len | Len |
| 20 | GIU | Olu | 275 | | цуБ | Deu | niu | 280 | 1100 | 71.4 | nsp | O L y | 285 | 1110 | u | Deu |
| | 7 ~~~ | 61 m | | 7 0 | 7 | 000 | 1 011 | | G1 | П | 1707 | T 011 | | T 011 | 17-1 | uio |
| | Arg | | Cys | Leu | Arg | 361 | | GLY | GTA | гÄт | val | | ser | Leu | vai | піз |
| | _ | 290 | _ | 1 | | | 295 | _ | | | _ | 300 | _ | _ | ~3 | |
| 05 | - | vaı | Arg | Pne | HIS | | Pne | Pro | TIE | Gru | | GIN | ьеu | Asn | GIY | |
| 25 | 305 | | - | | | 310 | _ | | | | 315 | | | | _ | 320 |
| | Tyr | Ala | Ile | Ala | _ | GIA | ьуs | Ala | His | _ | GIA | Pro | Ala | Glu | | Cys |
| | _ | | | | 325 | | | | _ | 330 | | | | | 335 | |
| | GLu | Phe | Tyr | | Arg | Asp | Pro | Asp | | Leu | Pro | Cys | Asn | | Arg | Lys |
| | | | | 340 | | | | | 345 | | | | | 350 | | |
| 30 | Pro | Cys | Asn | Arg | Pro | Ser | Gly | Leu | Glu | Pro | Gln | Pro | Gly | Val | Phe | Asp |
| | | | 355 | | | | | 360 | | | | | 365 | | | |
| | Cys | Leu | Arg | Asp | Ala | Met | Val | Arg | Asp | Tyr | Val | Arg | Gln | Thr | Trp | Lys |
| | | 370 | | | | | 375 | | | | | 380 | | | | |
| | Leu | Glu | Gly | Glu | Ala | Leu | Glu | Gln | Ala | Ile | Ile | Ser | Gln | Ala | Pro | Gln |
| 35 | 385 | | | | | 390 | | | | | 395 | | | | | 400 |
| | Val | Glu | Lys | Leu | Ile | Ala | Thr | Thr | Ala | His | Glu | Arq | Met | Pro | Trp | Tyr |
| | | | - | | 405 | | | | | 410 | | _ | | | 415 | _ |
| | His | Ser | Ser | Leu | Thr | Arq | Glu | Glu | Ala | Glu | Arg | Lvs | Leu | Tvr | Ser | Gly |
| | | | | 420 | | | | | 425 | | | | | 430 | | • |
| 40 | Ala | Gln | Thr | Asp | Glv | Lvs | Phe | Leu | | Ara | Pro | Ara | Lvs | Glu | Gln | Glv |
| , • | | 01 | 435 | P | 1 | -,- | | 440 | | 9 | | *** 5 | 445 | | | 4 -7 |
| | Thr | Tur | Ala | T.OU | Ser | T.011 | Tle | | Glv | Lve | Thr | Val | | Hic | Tur | T.em |
| | 1111 | 450 | Y10 | neu | SCL | БСи | 455 | LYL | Gry | цуб | 1111 | 460 | TYL | 1115 | ryr | шси |
| | T1- | | ~1 - | 7 ~~ | T | 77. | | T | m | <i>a</i> | 71 = | | ~1 | G1 | mb | T 110 |
| A.E. | | 261 | Gln | Asp | _ | | GIA | nys | IYL | Cys | | PIO | GIU | GIY | 1111 | |
| 45 | 465 | | | | | 470 | | | ~1 | _ | 475 | | - | - | | 480 |
| | Pne | Asp | Thr | ьeu | | Gin | Leu | vaı | GIU | | ьeu | гàг | ьeu | гàг | | Asp |
| | | _ | | _ | 485 | _ | _ | | | 490 | | _ | _ | _ | 495 | _ |
| | Gly | Leu | Ile | - | Cys | Leu | Lys | Glu | | Cys | Pro | Asn | Ser | | Ala | Ser |
| | | | | 500 | | | | | 505 | | | | | 510 | | |
| 50 | Asn | Ala | ser | Gly | Ala | Ala | Ala | Pro | Thr | Leu | Pro | Ala | His | Pro | Ser | Thr |
| | | | 515 | | | | | 520 | | | | | 525 | | | |
| | Leu | Thr | His | Pro | Gln | Arg | Arg | Ile | Asp | Thr | Leu | Asn | Ser | Asp | Gly | Tyr |
| | | 530 | | | | | 535 | | | | | 540 | | | | |
| | Thr | Pro | Glu | Pro | Ala | Arg | Ile | Thr | Ser | Pro | Asp | Lys | Pro | Arg | Pro | Met |
| 55 | 545 | | | | | 550 | | | | | 555 | | | | | 560 |
| | Pro | Met | Asp | Thr | Ser | Val | Tyr | Glu | Ser | Pro | Tyr | Ser | Asp | Pro | Glu | Glu |

198

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565
                                           570
        Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                            585
        Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
   5
                                   600
        Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
                                                      605
                              615
        Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                                                  620
                          630
                                               635
        Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
  10
                                          650
       Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly
                                    665
       Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
  15
                                 680
       Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                               695
       Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                          710
                                             715
 20
       Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
                                 730
       Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                   740
                                     745
       Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
 25
                                  760
       Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                            775
                                                  780
      Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                         790
                                             795
      Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
 30
                                         810
      Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                  820
                                      825
      Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
 35
                                 840
      Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
                                                    845
                           855
                                                860
      Lys Ala Glu Ala Ala Cys Ala
                         870
40
               (2) INFORMATION FOR SEQ ID NO:110:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2598 base pairs
45
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
50
            (ix) FEATURE:
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2595
               (D) OTHER INFORMATION:
55
```

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

. 199

| 5 | | CCC Pro | | | | | | _ | | 48 |
|----|--|-------------------|--|--|--|--|---|---|---|-----|
| J | | GCC Ala 20 | | | | | | | _ | 96 |
| 10 | | CTG Leu | | | | | | _ | | 144 |
| 15 | | CAC His | | | | | | | _ | 192 |
| 20 | | ACC Thr | | | | | | _ | | 240 |
| 25 | | TGC Cys | | | | | _ | | | 288 |
| | | AAG Lys 100 | | | | | | _ | | 336 |
| 30 | | GAC Asp | | | | | | _ | | 384 |
| 35 | | AAG Lys | | | | | | _ | | 432 |
| 40 | | CAG Gln | | | | | | _ | | 480 |
| 45 | | TAC Tyr | | | | | | | | 528 |
| | | GGG Gly 180 | | | | | | | | 576 |
| 50 | | GGC Gly | | | | | | | | 624 |
| 55 | | CTC Leu | | | | | | | | 672 |

| 5 | GAG GGC ACC AAG TTT GAC ACG CTC TGG CAG CTG GTG GAG TAT CTG AAG Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys 230 CTG AAG GCG GAC GGG CTC ATC TAC TGC CTG AAG GAG GCC TGC CCC AAC Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn | 720 768 |
|----|--|------------|
| 10 | 245 250 255 AGC AGT GCC AGC AAC GCC TCA GGG GCT GCT GCT CCC ACA CTC CCA GCC Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala 260 260 265 270 | 816 |
| 15 | CAC CCA TCC ACG TTG ACT CAT CCT CAG AGA CGA ATC GAC ACC CTC AAC His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn 275 280 285 | 864 |
| 20 | TCA GAT GGA TAC ACC CCT GAG CCA GCA CGC ATA ACG TCC CCA GAC AAA Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys 290 295 300 | 912 |
| 25 | CCG CGG CCG ATG CCC ATG GAC ACG AGC GTG TAT GAG AGC CCC TAC AGC Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser 310 315 320 | 960 |
| 20 | GAC CCA GAG GAG CTC AAG GAC AAG AAG CTC TTC CTG AAG CGC GAT AAC Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn 325 330 335 | 1008 |
| 30 | CTC CTC ATA GCT GAC ATT GAA CTT GGC TGC GGC AAC TTT GGC TCA GTG Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val 340 345 350 | 1056 |
| 35 | CGC CAG GGC GTG TAC CGC ATG CGC AAG AAG CAG ATC GAC GTG GCC ATC Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile 355 360 365 | 1104 |
| 40 | AAG GTG CTG AAG CAG GGC ACG GAG AAG GCA GAC ACG GAA GAG ATG ATG Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met 370 375 380 | 1152 |
| 45 | CGC GAG GCG CAG ATC ATG CAC CAG CTG GAC AAC CCC TAC ATC GTG CGG Arg Glu Ala Gln Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg 390 395 400 | 1200 |
| 50 | CTC ATT GGC GTC TGC CAG GCC GAG GCC CTC ATG CTG GTC ATG GAG ATG Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met 405 410 415 | 1248 |
| | GCT GGG GGC GGG CCG CTG CAC AAG TTC CTG GTC GGC AAG AGG GAG GAG Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu 420 425 430 | 1296 |
| 55 | ATC CCT GTG AGC AAT GTG GCC GAG CTG CTG CAC CAG GTG TCC ATG GGG Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly 435 440 445 | 1344 |
| | | 200 |

| 5 | | | | GAG Glu | | | | | | 1392 |
|----|--|---|---|-------------------|--|--|--|--|--|------|
| J | | | | CTG Leu | | | | | | 1440 |
| 10 | | | | GCA Ala 485 | | | | | | 1488 |
| 15 | | | | TGG Trp | | | | | | 1536 |
| 20 | | | | TCC Ser | | | | | | 1584 |
| 25 | | _ | _ | TTG Leu | | | | | | 1632 |
| | | | | ATG Met | | | | | | 1680 |
| 30 | | _ | | CCA Pro 565 | | | | | | 1728 |
| 35 | | | | GAG Glu | | | | | | 1776 |
| 40 | | _ | | TAC Tyr | | | | | | 1824 |
| 45 | | | | AAG Lys | | | | | | 1872 |
| | | | | AGC Ser | | | | | | 1920 |
| 50 | | | | CTG Leu 645 | | | | | | 1968 |
| 55 | | | | GAG Glu | | | | | | 2016 |

202

| 5 | TTC AT | 675 | 5 | | CI, I | 61 61 | 30 30 | o val | l Pro | Trp | Pro 685 | Thr | Le | u Val | 2064 |
|----|---------------------------|----------------|----------------|----------------------|-----------------------|----------------|------------|-----------------------|----------------|----------------------|--------------|------------|--------------|------------|------|
| | ACC AC Thr Th 69 | 0 | | -1- | 6 | 95 | т су | s Pne | Ser | Arg 700 | Tyr | Pro | Ası |) His | 2112 |
| 10 | ATG AA Met Ly 705 | | | ···p | 710 | пе Бу | s se | r Ala | 715 | Pro | Glu | Gly | Tyr | 720 | 2160 |
| 15 | CAG GAG Gln Glu | J | | 725 | inc P | ие гу | s Asp | 730 | GIY | Asn ' | Tyr | Lys | Thr 735 | Arg | 2208 |
| 20 | GCC GAC Ala Glu | | 740 | | Jau G. | LY AS | 745 | Leu | Val | Asn A | Arg : | Ile 750 | Glu | Leu | 2256 |
| 25 | AAG GGC Lys Gly | 755 | | | ., 5 01 | 760 |) | Asn | 11e | Leu C | 31y 1 765 | lis . | Lys | Leu | 2304 |
| | GAG TAC Glu Tyr 770 | | 1 - 3. | 0 | 77 | 5 ASI | ı vaı | ıyr | Ile i | Met A 780 | la A | sp 1 | Lys | Gln | 2352 |
| 30 | AAG AAC Lys Asn 785 | • | | 75 | 90 | n Phe | ьуs | ile . | Arg 1 795 | dis A | sn I | le C | 3lu | Asp 800 | 2400 |
| 35 | GGC AGC Gly Ser | GTG (| CAG C Gln L | TC G(eu A] 05 | CC GA | C CAC P His | TAC Tyr | CAG (Gln (810 | CAG A Gln A | AAC A | CC C hr P | ro I | TC le | GGC Gly | 2448 |
| 40 | GAC GGC Asp Gly | 8 | 320 | Ju Do | .u F1(| Asp | 825 | His 7 | Tyr L | eu Se | er Th | nr G 30 | ln a | Ser | 2496 |
| 45 | GCC CTG Ala Leu | 835 | 1 | ·F | O ASI | 840 | nys . | Arg A | Asp H | is Me 84 | et Va 5 | ıl L | eu I | Leu | 2544 |
| | GAG TTC Glu Phe 850 | GTG A Val T | CC GC | CC GC | C GGG a Gly 855 | ATC Ile | ACT (| CTC G Leu G | TA We | TG GA et As 60 | C GA | G C' | rg 7 eu 7 | TAC Tyr | 2592 |
| 50 | AAG TAA Lys 865 | | | | | | | | | | | | | | 2598 |

55 (2) INFORMATION FOR SEQ ID NO:111:

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(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 865 amino acids
```

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- 5 (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn

Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val

Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile

| | 204 | |
|----|--|---|
| | 355 | |
| | Lys Val Ley Lys Gln Cly mby Gl | |
| | Lys Val Leu Lys Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met 370 375 380 | t |
| 5 | 385 390 Ala Gin Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg | 3 |
| | Leu Ile Gly Val Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met |) |
| | Ala Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys Arg Cly Gly | |
| 10 | 420 425 430 Ile Pro Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly 435 | ı |
| | 435 440 445 Met Lys Tyr Leu Glu Glu Lys App Di 1915 Gin val Ser Met Gly | • |
| | Met Lys Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala 450 455 460 | |
| 15 | Arg Asn Val Leu Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe | |
| | GIY Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg | |
| | Ser Ala Gly Lys Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn | |
| 20 | Phe Arg Lys Phe Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr | |
| | Met Trp Glu Ala Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys | |
| 25 | Gly Pro Glu Val Met Ala Phe Ile Glu Gln Gly Lys Arg Met Gly Cro | |
| | 545 550 555 560 | |
| | Pro Pro Glu Cys Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp 565 570 | |
| | 11e Tyr Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg | |
| 30 | Met Arg Ala Cys Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro | |
| | Gly Ser Thr Gln Lys Ala Glu Ala Ala Cys Ala Trp Asp Pro Pro Val | |
| 35 | Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro | |
| 33 | 630 635 640 Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val | |
| | 645 650 655 Ser Gly Glu Gly App Ala Thur | |
| 40 | Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys 660 665 665 670 | |
| | Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val 675 680 685 | |
| | Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His 690 695 | |
| 45 | Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val | |
| | Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg | |
| | Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asp Arg Llo Gly Leu | |
| 50 | Lys Gly Ile Asp Phe Lys Glu Asp Gly Asp Ile Low Gly Wile 7 | |
| | 755 760 765 Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln 770 775 | |
| | Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp 785 790 | |
| 55 | 785 790 795 800 | |
| | Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly | |

| | Asp | Gly | Pro | Val 820 | 805 Leu | Leu | Pro | Asp | Asn 825 | 810 His | Tyr | Leu | Ser | Thr 830 | 815 Gln | Ser | | |
|----|------------|------------|-------------------|---------------------|---|------------------------|-----------------------|-----------------------|------------|------------|------|------------|------------|-------------------|------------|-----|-----|-----|
| 5 | Ala | Leu | Ser 835 | | Asp | Pro | Asn | Glu 840 | | Arg | Asp | His | Met 845 | Val | Leu | Leu | | |
| | Glu | Phe 850 | | Thr | Ala | Ala | Gly 855 | | Thr | Leu | Gly | Met 860 | | Glu | Leu | Tyr | | |
| 10 | Lys 865 | | | | | | | | | | | | | | | | | |
| | | | (2) | INI | FORM | MIOITA | 1 FOF | SEC |) ID | NO: | 112: | | | | | | | |
| 15 | | (i) | (A) (B) (C) | LENG TYPE STR | NCE (STH: E: nu NDEI OLOGY | 1639 uclei ONESS | bas ic ac S: si | se pa cid ingle | airs | | | | | | | | | |
| 20 | | | | OLEC | TULE JRE: | TYPI | E: CI | ONA | | | | | | | | | | |
| 25 | | | (B) | LO | ME/KE CATIO MER I | ON: I | l] | L632 | equer | nce | | | | | | | | |
| 25 | | () | ki) S | EQUE | ENCE | DESC | CRIPT | CION | : SE(| Q ID | NO: | 112: | | | | | | |
| 30 | | | | | | | | | | | | | | ACG Thr | | | 48 | |
| | | | | | | | | | | | | | | GTG Val 30 | | | 96 | |
| 35 | | | | | | | | | | | | | | AGT Ser | | _ | 144 | |
| 40 | | | | | | | | | | | | | | AAT Asn | | | 192 | |
| 45 | | | | | | | | | | | | | | CTG Leu | | | 240 | |
| 50 | | | | | | | | | | | | | | TCT Ser | | | 288 | |
| 55 | | | | | | | | | | | | | | CAG Gln 110 | | | 336 | |
| Jü | CAG | GGC | СТА | GCT | TTC | TGC | CAT | TCT | CAT | CGG | GTC | CTC | CAC | CGA | GAC | CTT | 384 | 205 |

| | | | | | | | | | | 200 | | | | | | | |
|----|-------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|-----------------------|--------------------|--------------------|-----------------------|-----------------------|-----------------------|--------------------|---------------------|-------------|
| | G] | ln G | ly L 1 | eu A: 15 | la Pł | ne Cy | s Hi | .s Se 12 | r Hi | s Aı | rg Va | al Le | eu Hi 12 | | g A | sp Leu | |
| 5 | AA Ly | | CT C ro G 30 | AG A# ln As | AT CI sn Le | G CT u Le | T AT u Il 13 | e As | C AC | A GA r Gl | G GG u Gl | SG GC Ly Al | a Il | C AA e Ly | G CT | TA GCA u Ala | 432 |
| 10 | GA As 14 | £ | rr G(ne G] | GA CI ly Le | A GC u Al | C AG a Ar 15 | A MI | T TT a Ph | T GG e Gl | A GT y Va | C CC 1 Pr 15 | o Va | T CG | T AC g Th | Т ТА г Ту | C ACC T Thr | 480 |
| 15 | CA' Hi | T GA s Gl | G GI u Va | TG GT | G AC 1 Th 16 | т пе | 3 TG0 u Tr) | G TAC | C CG | A GC g Al 17 | a Pr | T GA o Gl | A ATO | C CT | C CT u Le 17 | G GGC u Gly 5 | 528 |
| | TC(Se | G AA r Ly | A TA | T TA T Ty 18 | . DC. | C ACA | A GCT | r GTC | G GAG L Asp 185 | o Ile | C TG | G AG | C CTO | G GG(1 Gly 19(| у Су | C ATC | 576 |
| 20 | TTT Phe | r GC e Al | T GA a Gl | | G GTO | G ACT l Thr | CGC Arg | CGG J Arg 200 | l ATS | C CTO | TTO Phe | C CC | r GGF O Gly 205 | Asp | TC' Se: | r GAG r Glu | 624 |
| 25 | ATT Ile | GA6 Asp | | G CT(n Lei | TTC Phe | CGG Arg | Ile 215 | Pne | CGG Arg | ACT Thr | CTC | G GGC 1 Gly 220 | Thr | CCA Pro | GAT Asp | GAG Glu | 672 |
| 30 | GTG Val 225 | - | TGC Trp | G CCA | A GGA O Gly | GTT Val 230 | ACT Thr | TCT Ser | ATG Met | CCT Pro | GAT Asp 235 | Tyr | AAG Lys | CCA Pro | AGT Ser | TTC Phe 240 | 720 |
| 35 | CCC Pro | AAC Lys | TGG Trp | GCC Ala | CGG Arg 245 | CAA Gln | GAT Asp | TTT Phe | AGT Ser | AAA Lys 250 | GTT Val | ' GTA Val | CCT Pro | CCC Pro | CTG Leu 255 | GAT Asp | 768 |
| | GAA Glu | GAT Asp | GGA Gly | CGG Arg 260 | AGC Ser | TTG Leu | TTA Leu | TCG Ser | CAA Gln 265 | ATG Met | CTG Leu | CAC His | TAC Tyr | GAC Asp 270 | CCT Pro | AAC Asn | 816 |
| 40 | AAG Lys | CGG Arg | ATT Ile 275 | JCI | GCC Ala | AAG Lys | GCA Ala | GCC Ala 280 | CTG Leu | GCT Ala | CAC His | CCT Pro | TTC Phe 285 | TTC Phe | CAG Gln | GAT Asp | 864 |
| 45 | GTG Val | ACC Thr 290 | AAG Lys | CCA Pro | GTA Val | CCC Pro | CAT His 295 | CTT Leu | CGA Arg | CTC Leu | TGG Trp | GAT Asp 300 | CCA Pro | CCG Pro | GTC Val | GCC Ala | 912 |
| 50 | ACC Thr 305 | ATG Met | GTG Val | AGC Ser | AAG Lys | GGC Gly 310 | GAG Glu | GAG Glu | CTG Leu | TTC Phe | ACC Thr 315 | GGG Gly | GTG Val | GTG Val | CCC Pro | ATC Ile 320 | 960 |
| 55 | CTG Leu | GTC Val | GAG Glu | CTG Leu | GAC Asp 325 | GGC Gly | GAC Asp | GTA . Val . | Asn | GGC Gly 330 | CAC His | AAG Lys | TTC . Phe | Ser | GTG Val 335 | TCC Ser | 1008 |
| | GGC | GAG | GGC | GAG | GGC | GAT (| GCC / | ACC ' | TAC (| GGC . | AAG | CTG | ACC (| | | TTC | 1056 206 |

207

| | Gly | Glu | Gly | Glu 340 | Gly | Asp | Ala | Thr | Tyr 345 | Gly | Lys | Leu | Thr | Leu 350 | Lys | Phe | | |
|----|-----|-----|-----|------------|-----|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|------------|---|------|
| 5 | | | | | | AAG Lys | | | | | | | | | | | | 1104 |
| 10 | | | | | | GTG Val | | | | | | | | | | | | 1152 |
| 15 | | | | | | TTC Phe 390 | | | | | | | | | | | | 1200 |
| 15 | | | | | | TTC Phe | | | | _ | | | | | | | | 1248 |
| 20 | | | | | | GGC Gly | | | | | | | | | | | | 1296 |
| 25 | | | | | | GAG Glu | | | | | | | | | | | | 1344 |
| 30 | | | | | | CAC His | | | | | | | | | | | | 1392 |
| 35 | | | | | | AAC Asn 470 | | | | | | | | | | | | 1440 |
| 35 | | | | | | GAC Asp | | | | | | | | _ | _ | | | 1488 |
| 40 | | | | | | CCC Pro | | | | | | | | | | | | 1536 |
| 45 | | | | | | AAC Asn | | | | | | | | | | | | 1584 |
| 50 | | | | | | GGG Gly | | | | | | | | | | AAG Lys | т | 1633 |
| | AA | | | | | | | | | | | | | | | | | 1635 |

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 544 amino acids
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- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Met Glu Asn Phe Gln Lys Val Glu Lys Ile Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu Gly Val Pro Ser Thr Ala Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Asn His Pro Asn Ile Val Lys Leu Leu Asp Val Ile His Thr Glu Asn Lys Leu Tyr Leu Val Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser Tyr Leu Phe Gln Leu Leu Gln Gly Leu Ala Phe Cys His Ser His Arg Val Leu His Arg Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys Leu Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Val Pro Val Arg Thr Tyr Thr His Glu Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Ile Leu Leu Gly Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile Trp Ser Leu Gly Cys Ile Phe Ala Glu Met Val Thr Arg Arg Ala Leu Phe Pro Gly Asp Ser Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr Leu Gly Thr Pro Asp Glu Val Val Trp Pro Gly Val Thr Ser Met Pro Asp Tyr Lys Pro Ser Phe Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys Val Val Pro Pro Leu Asp Glu Asp Gly Arg Ser Leu Leu Ser Gln Met Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu Trp Asp Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr

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| | Thr | Leu 370 | Thr | Tyr | Gly | Val | Gln 375 | Cys | Phe | Ser | Arg | Tyr 380 | Pro | Asp | His | Met | |
|-----|------------|------------|-----------|------------|----------------|------------|------------|-----------|------------|------------|------------|------------|-----------|------------|------------|------------|-----|
| | Lys 385 | _ | His | Asp | Phe | Phe 390 | | Ser | Ala | Met | | | Gly | Tyr | Val | | |
| 5 | | Arg | Thr | Ile | Phe | | Lys | Asp | Asp | | 395 Asn | Tyr | Lys | Thr | | 400 Ala | |
| | Glu | Val | Lys | Phe | 405 Glu | Gly | Asp | Thr | Leu | 410 Val | Asn | Arg | Ile | Glu | 415 Leu | Lys | |
| | Glv | Ile | Asp | 420 Phe | Lys | Glu | Asp | Glv | 425 Asn | Ile | Leu | Glv | His | 430 Lvs | Leu | Glu | |
| 10 | | | 435 | | | | | 440 | | | | _ | 445 | | | | |
| | Tyr | 450 | Tyr | Asn | Ser | HIS | 455 | vaı | Tyr | TTE | Met | A1a 460 | Asp | Lys | GIn | Lys | |
| | Asn 465 | Gly | Ile | Lys | Val | Asn 470 | Phe | Lys | Ile | Arg | His 475 | Asn | Ile | Glu | Asp | Gly 480 | |
| 15 | Ser | Val | Gln | Leu | Ala 485 | Asp | His | Tyr | Gln | Gln 490 | Asn | Thr | Pro | Ile | Gly 495 | Asp | |
| | Gly | Pro | Val | | Leu | Pro | Asp | Asn | | | Leu | Ser | Thr | | | Ala | |
| | Leu | Ser | Lys | 500 Asp | Pro | Asn | Glu | Lys | 505 Arg | Asp | His | Met | Val | 510 Leu | Leu | Glu | |
| 20 | Dho | Wa I | 515 | 777 | Ala | Cly | Tlo | 520 | Lou | C1 | Mot | 7 an | 525 | T 011 | Tire | Tvo | |
| | PHE | 530 | 1111 | Ala | міа | GIY | 535 | 1111 | beu | Gry | Mec | 540 | GIU | пеп | ıyı | Буѕ | |
| | | | (2) | INI | FORM | TION | 1 FOI | R SE | QI Ç | NO: | 114: | | | | | | |
| 25 | | () | i) SI | eouri | NCE (| ימממי | ושרטבו | י ביי | ירפי | | | | | | | | |
| | | () | (A) | LENG | GTH: | 1635 | bas | se pa | | | | | | | | | |
| | | | | | E: ni ANDEI | | | | 2 | | | | | | | | |
| 30 | | | | | DLOG | | | - | | | | | | | | | |
| | | | | OLEC | CULE JRE: | TYPI | E: cI | ONA | | | | | | | | | |
| 35 | | | (A) | NAI | ME/KE | EY: (| Codir | ng Se | equer | nce | | | | | | | |
| | | | | | CATIO | | | | | | | | | | | | |
| | | (2 | (i) S | EQUI | ENCE | DESC | CRIPT | rion | : SE(|) ID | NO: | 114: | | | | | |
| 40 | ATG | GTG | AGC | ΔAG | GGC | GAG | GAG | CTG | ጥጥር | ACC | GGG | GTG | GTG | CCC | ልጥሮ | כידני | 48 |
| | Met | | | | Gly | | | | | Thr | | | | | Ile | | 10 |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| 45 | | | | | GGC Gly | | | | | | | | | | | | 96 |
| | vai | GIU | Deu | 20 | GLY | rap | Val | Maii | 25 25 | nis | пуз | FIIC | 261 | 30 | 261 | Gry | |
| | GAG | GGC | GAG | GGC | GAT | GCC | ACC | TAC | GGC | AAG | CTG | ACC | CTG | AAG | TTC | ATC | 144 |
| 50 | Glu | Gly | Glu 35 | Gly | Asp | Ala | Thr | Tyr 40 | Gly | Lys | Leu | Thr | Leu 45 | Lys | Phe | Ile | • |
| | TGC | ACC | ACC | GGC | AAG | CTG | CCC | GTG | CCC | TGG | כככ | ACC | СТС | GTG | ACC | ACC | 192 |
| E E | | Thr | | | Lys | | Pro | | | | | Thr | | | | | |
| 55 | | 50 | | | | | 55 | | | | | 60 | | | | | |

| | | | | | | | | | | | | 21 | | | | | | | | | | |
|----|-------------------|------------|----------------|-----------------|-------------------|--------------------|------------|------------|------------------|-------------|--------------------|-------------------|------------|-------------------|--------------|--------------|-------------------|-----------------|--------------|------------|-----------|-----|
| - | 6 | 5 | | • | | GC G Ly V | 7 | 0 | -ys | PHE | : Se | r A | rg 1 | Tyr 75 | Pro |) As | p i | lis | Me | t : | Lys 80 | 240 |
| 5 | | | | • | | C T ie Pl 8! | 5 | y 5 . | CI | HIG | и ме | 9(| .co G | ilu | Gly | ту | r V | al | G1: 95 | n (| Glu | 288 |
| 10 | | _ | | | 10 | | | узн | .sp | Авр | 10 | y As 5 | n T | yr | Lys | Th | r A 1 | rg 10 | Ala | a (| 3lu | 336 |
| 15 | | | • | 115 | | G GG u Gl | ·y A | op 1 | : | 120 | val | L AS | n A | rg | Ile | Gl: | ı L | eu | Lys | 3 G | ly | 384 |
| 20 | | 13 | 30 | | -1 | G GA 5 Gl | ~ /I. | 1: | 35 | na <i>F</i> | 116 | : ье | u G. | Ly : | His 140 | Lys | : Le | eu | Glu | T | yr | 432 |
| | 14 | 5 | • | | | CA Hi | 15 | 0 | 11 1 | ΥΥ | тте | Me | 15 | la <i>1</i> 55 | Asp | Lys | G] | n i | Lys | A: | sn 60 | 480 |
| 25 | _ | | | - . - | | AA Ası 165 | 5 | с пу | SI | те | Arg | H15 | As) | n] | lle | Glu | As | p (| 31y 175 | Se | er | 528 |
| 30 | | | | | 180 | | , | 3 I Y | ı G | III · | GIN 185 | Asn | Th | r F | ro | Ile | Gl 19 | у <i>Р</i> 0 | Asp | G1 | У | 576 |
| 35 | | | 1 | 95 | | CCC | 11.01 | , AS | 20 | 00 | ryr | ren | Se | r T | hr (| Gln 205 | Se | r A | la | Le | u | 624 |
| 40 | | 210 | 0 | • | | AAC Asn | 010 | 21! | 5 S A1 | g A | qaA | HIS | Met | 2 V | al I 20 | Leu | Le | 1 G | lu | Ph | е | 672 |
| | GTG Val 225 | | | | | U ., | 230 | 1111 | . Le | eu c | яТĀ | Met | 235 |) G | lu I | eu | Туз | L | ys : | Se: | r O | 720 |
| 45 | GGA Gly | CTC | A) | GA : | rcr Ser | CGA Arg 245 | GCC Ala | ATC Met | GA Gl | G A | sn | TTC Phe 250 | CAA Gln | A.Z | AG G vs V | TG al | GAA Glu | L | AG 2 ys : | ATC | 2 | 768 |
| 50 | GGA Gly | GAG Glu | GG G1 | - | ACG Thr 160 | TAC Tyr | GGA Gly | GTT Val | ' GT Va | 1 T | AC 2 yr 1 65 | AAA Lys | GCC Ala | Ar | A A | sn : | AAG Lys 270 | Le | rg A | ACG Thr | 3 : | 816 |
| 55 | GGA Gly | GAG Glu | GT Va 27 | G G 1 V 5 | TG (| GCG Ala | CTT Leu | AAG Lys | AA Lys 280 | S I. | TC (| CGC Arg | CTG Leu | GA As | p T | CT (hr (| GAG Glu | AC | T G | GAG Slu | ; | 864 |

| | | | | | | 211 | | | | | |
|----|--|---|-------------------|--|---|------|------|--|---|---|------|
| | | | ACT Thr | | | | | | | | 912 |
| 5 | | | ATT Ile | | | | | | | | 960 |
| 10 | | | GTT Val 325 | | | | | | | | 1008 |
| 15 | | | GCT Ala | | | | | | | | 1056 |
| | | | CTG Leu | | | | | | | | 1104 |
| 20 | | | GAC Asp | | | | | | | | 1152 |
| 25 | | | CTA Leu | | | | | | | | 1200 |
| 30 | | | TAC Tyr 405 | | _ | | | | | _ | 1248 |
| 35 | | | CTG Leu | | | | | | | _ | 1296 |
| 40 | | | TGC Cys | | | | | | _ | | 1344 |
| 40 | | | TCT Ser | | | | | | | | 1392 |
| 45 | | | GAT Asp | | | | | | | | 1440 |
| 50 | | _ | AGT Ser 485 | | | | | | | | 1488 |
| 55 | | | CTG Leu | | | | | | | | 1536 |

| | | | | | | | | | | 21 | | | | | | | | |
|------------|------------|--------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------|----------------------|-----------|----------------|------------|----------------|--------------------|-----------|------------------|---|------|
| | CT Le | CG C | | AC GI yr A: 15 | AC Co | CT A. | ac A | ys Al | GG A' rg I: 20 | TT To | CG G er A | CC A | ys A | CA G la A 25 | CC C | TG GCT eu Ala | | 1584 |
| 5 | CA Hi | C CC s Pr 53 | | rc Ti | rc ca ne Gl | AG GA | SP V | rg ac al Th | CC AA | AG CO | CA G: ro Va | al Pi | CC CA ro H: | AT C | FT CC | GA CTC f | т | 1633 |
| 10 | GA | | , | ד נכי | NEOD | Mስጥነ | -ON F | .05 | | _ | | | | | | | | 1635 |
| | | | , | 2, 1 | MEOR | I LAM | .ON F | OR S | EQ I | D NC |):115 | : | | | | | | |
| 15 | | | (A (B (C |) TY | NGTH PE: RAND | : 54 amin EDNE | 4 am o ac SS: | sing | acid | s: | | | | | | | | |
| 20 | | | (ii) (v) | MOL FRAG | ECUL MENT | Е ТҮ ТҮР | PE: E: i | prote | ein nal | | | | | | | | | |
| | | | (xi) | SEQ | JENC | E DE | SCRI | PTIO | N: S | EO TI | р ио | .115 | | | | | | |
| 25 | Met 1 | | | | s Gly | | | | | | | | | l Pro | o Ile | e Leu | | |
| 20 | | | | | | | | | ı Gly | | | | | | | c Gly | | |
| | | | / Glu | | | | | туг | | | | | | 20 | | e Ile | | |
| 30 | | | | | | | | 40 | | | | Thi | | | | Thr | | |
| | Leu 65 | Thr | Туг | Gly | Val | Glr 70 | Cys | Phe | Ser | Arg | Tyr | 60 Pro | Asp | His | Met | Lys | | |
| 35 | Gln | His | Asp | Phe | Phe 85 | | Ser | Ala | Met | Pro | 75 Glu | Gly | туг туг | Val | Gln | 80 Glu | | |
| | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | 90 Asn | туг | Lys | Thr | Arg | 95 Ala | Glu | | |
| | Val | Lys | Phe 1 1 5 | Glu | Gly | Asp | Thr | Leu 120 | Val | Asn | Arg | Ile | | | Lys | Gly | | |
| 40 | Ile | Asp 130 | Phe | Lys | Glu | Asp | Gly 135 | Asn | Ile | Leu | Gly | His | 125 Lys | Leu | Glu | Tyr | | |
| | Asn 145 | Tyr | Asn | Ser | His | Asn 150 | Val | Tyr | Ile | Met | Ala | 140 Asp | Lys | Gln | Lys | Asn | | |
| 45 | | | | | | Phe | | Ile | | | | | | | | | | |
| | | | | | | | | Gln | Gln | Asn | Thr | | | | | | | |
| | Pro | | | | | | | | Tyr | | | | | | | | | |
| 50 | | | | | | | | Arg | | | | | | | | | | |
| | Val 225 | | | | | | Thr | | | | | | | | | | | |
| F F | Gly : | Leu | Arg | Ser | Arg | Ala | Met | Glu | Asn | Phe | 235 Gln | Lve | Val | Gl | T > - ~ | 240 Tlo | | |
| 55 | Gly (| | | | | | | | | | | | | | | | | |
| | | | | | | _ | | - | | _, . | | • 3 L G | ASII | ьys | ьeи | inr | | |

213

| | | | | | | | | | | 213 | | | | | | |
|----|------------|------------|------------|-------------------------------|---------------|---------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | | | | 260 | | | | | 265 | | | | | 270 | | |
| | Gly | Glu | Val 275 | Val | Ala | Leu | Lys | Lys 280 | Ile | Arg | Leu | Asp | Thr 285 | Glu | Thr | Glu |
| 5 | Gly | Val 290 | | Ser | Thr | Ala | Ile 295 | | Glu | Ile | Ser | Leu 300 | | Lys | Glu | Leu |
| J | | | Pro | Asn | Ile | | | Leu | Leu | Asp | | | His | Thr | Glu | |
| | 305 | | M | T | 17-1 | 310 | 01 | D1 | T | *** - | 315 | 3 | | . | T | 320 |
| | | | | | 325 | | | | | 330 | | | | | Lys 335 | |
| 10 | Met | Asp | Ala | Ser 340 | Ala | Leu | Thr | Gly | Ile 345 | Pro | Leu | Pro | Leu | 11e 350 | Lys | Ser |
| | Tyr | Leu | Phe 355 | Gln | Leu | Leu | Gln | Gly 360 | Leu | Ala | Phe | Cys | His 365 | Ser | His | Arg |
| 15 | Val | Leu 370 | | Arg | Asp | Leu | Lys 375 | | Gln | Asn | Leu | Leu 380 | | Asn | Thr | Glu |
| | - | | Ile | Lys | Leu | | | Phe | Gly | Leu | | | Ala | Phe | Gly | Val 400 |
| | 385 Pro | Val | Arg | Thr | - | 390 Thr | His | Glu | Val | | 395 Thr | Leu | Trp | Tyr | Arg | |
| 20 | Pro | Glu | Ile | | 405 Leu | Gly | Ser | Lys | - | 410 Tyr | Ser | Thr | Ala | | 415 Asp | Ile |
| | Trp | Ser | | 420 Gly | Cys | Ile | Phe | | 425 Glu | Met | Val | Thr | _ | 430 Arg | Ala | Leu |
| | Phe | Pro | 435 Gly | Asp | Ser | Glu | Ile | 440 Asp | Gln | Leu | Phe | Arg | 445 Ile | Phe | Arg | Thr |
| 25 | Leu | 450 Gly | Thr | Pro | Asp | Glu | 455 Val | Val | Trp | Pro | Gly | 460 Val | Thr | Ser | Met | Pro |
| | 465 | _ | | | _ | 470 | | | _ | | 475 | | | | Ser | 480 |
| 20 | _ | - | - | | 485 | | | _ | - | 490 | _ | | _ | | 495 | |
| 30 | Val | Val | Pro | Pro 500 | Leu | Asp | GIu | Asp | G1y | Arg | Ser | Leu | Leu | 5er | Gln | Met |
| | Leu | His | Tyr 515 | Asp | Pro | Asn | Lys | Arg 520 | Ile | Ser | Ala | Lys | Ala 525 | Ala | Leu | Ala |
| 35 | His | Pro 530 | Phe | Phe | Gln | Asp | Val 535 | Thr | Lys | Pro | Val | Pro 540 | His | Leu | Arg | Leu |
| | | | (2) |) INI | FORM | ATIO | v FO | R SEG |) ID | NO: | 116: | | | | | |
| | | | | | | | | | _ | | | | | | | |
| 40 | | (: | (A) (B) | EQUEI LEN(TYPI STRI | GTH: E: ni | 2532 ucle: | 2 bas | se pa | airs | | | | | | | |
| | | | | TOP | | | | _ | - | | | | | | | |
| 45 | | | | MOLE FEAT | | TYPI | E: c | DNA | | | | | | | | |
| | | | |) NAI | | | | | eque | nce | | | | | | |
| 50 | | | • |) LO | - | | | | | | | | | | | |
| | | (: | xi) : | SEQU | ENCE | DES | CRIP' | TION | : SE | Q ID | NO: | 116: | | | | |
| | | | | | | | | | | | | | | | | |

213

48

15

10

ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

5

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.1

| 5 | | | | | 20 | P 01 | .у.ғ. | sp · | vaı | AS | 1 G. 25 | Ly 1 | His | Ly | s Pl | ne | Ser | . Va | l s | er | GGC Gly | 96 |
|----|-----------------------|------------------------|----------|------------------|-------------------|-------------------|--------------------|--------------------|------------|------------------|-------------------|----------------|--------------|-------------------|-------------------|----------------|------------------|-----------------|-------------------|------------|-------------------|-----|
| | GA G1 | G G | - | GAG Glu 35 | GG Gl | C GA y As | T G | CC A | ACC | TA(Ty) 40 | G GC | ic i | AAG Lys | CTo | G AC | ır | CTG Leu 45 | AA Ly | GT sP | TC he | ATC Ile | 144 |
| 10 | TG(Cy: | C A(s T) | | ACC Thr | G17 | C AA y Ly | G C | -u F | CCC Pro | GTC Val | CC Pr | C 1 | rgg Trp | CCC | C AC Th | ır] | CTC Leu | GT Va | G AG | cc | ACC Thr | 192 |
| 15 | CTC Let 65 | 3 AC | ec : | IAC Iyr | GGC Gly | C GT V Va | G CA 1 G1 70 | .11 C | 'GC | TTC | AG Se | C C | :GC .rg | TAC Tyr 75 | C CC | C (| SAC Asp | CA: | C AT | rg et | AAG Lys 80 | 240 |
| 20 | | | | F | | TTO Pho 85 | - шу | 5 5 | er | Ата | ме | t Р 9 | ro 0 | Glu | Gl; | уΊ | yr | Va] | 95 | n | Glu | 288 |
| 25 | J | | | | 100 | | : цу | S A | sp | Asp | 105 | γ A: 5 | sn | Tyr | Lys | з Т | hr | Arg 110 | Al | a | Glu | 336 |
| | | _, | 1 | 15 | oru | GGC | AS | 9 11 | ır . | 120 | val | L As | sn i | Arg | Ile | 2 G | 1u 25 | Leu | Ьγ | s (| Gly | 384 |
| 30 | ATC Ile | GAG As ₁ | | TC he | AAG Lys | GAG Glu | GA(| G GG G G1 13 | . у и | AAC Asn | ATC | CT Le | rg (eu (| GGG Gly | CAC His | L | AG Ys | CTG Leu | GA(| 3 7 u 1 | TAC Tyr | 432 |
| 35 | AAC Asn 145 | TAC | C A/ | AC . | AGC Ser | CAC His | AAC Asr 150 | ı va | C 1 | TAT Tyr | ATC Ile | AT Me | t A | GCC Ala 155 | GAC Asp | L) | AG (| CAG Gln | AAC Lys | s P | AAC Asn .60 | 480 |
| 40 | GGC Gly | ATC | Ly | AG (| GTG /al | AAC Asn 165 | TTC | Ly | G A s I | TC le | CGC Arg | CA Hi 17 | s A | AC sn | ATC Ile | GP G1 | .u A | GAC Asp | GGC Gly 175 | S | GC er | 528 |
| 45 | GTG Val | CAG Gln | Le | | SCC Ala .80 | GAC Asp | CAC His | TA: | C C | ın (| CAG Gln 185 | AA As: | C A | .cc hr | CCC Pro | AT Il | e G | GC 1y .90 | GAC Asp | G | GC ly | 576 |
| | CCC Pro | GTG Val | CT Le | | TG eu | CCC Pro | GAC Asp | AA(Asr | 1 H | AC ? is ? | rac ryr | CT(| G A | GC / | ACC Thr | CA G1 20 | n S | cc | GCC Ala | Ľ. | TG eu | 624 |
| 50 | AGC : | AAA Lys 210 | GA: | C C | cc i | AAC Asn | GAG Glu | AAC Lys 215 | A | GC (| SAT Asp | CAC His | C AT | et ' | GTC Val 220 | CT(| G C | TG eu | GAG Glu | T' | rc ne | 672 |
| 55 | GTG A Val 7 225 | ACC Thr | GC(| C G | CC (| - J | ATC Ile 230 | ACT Thr | CT Le | rc e | GC ly | ATC Met | G G# : As | sp G | GAG Glu | CT(| 3 T. | AC . yr : | AAG Lys | TO Se | er | 720 |
| | | | | | | | | | | | | | | | | | | | | | | 0.4 |

215

| | _ | | | | CGA | _ | | | | | | | | | | | 768 |
|-----|------|-----|------------|------------|------------|-------------|--------------|------------|------------|------|------|-----|------------|------------|------------|-------|------|
| 5 | GIY | Leu | Arg | ser | Arg 245 | GIU | met | Leu | ser | 250 | Gly | Trp | Phe | His | Arg 255 | Asp | |
| J | | | | | GAT | | | | | | | | | | | | 816 |
| | Leu | Ser | Gly | Leu 260 | Asp | Ala | Glu | Thr | Leu 265 | Leu | Lys | Gly | Arg | Gly 270 | Val | His | |
| 10 | | | | | GCT Ala | | | | | | | | | | | | 864 |
| | _ | | 275 | | | | | 280 | | - | | | 285 | _ | | | |
| 15 | | | _ | | GTG Val | _ | | | | | | | | | | | 912 |
| .0 | Deu | 290 | • • • • | ••• | | U 17 | 295 | 0111 | , | **** | **** | 300 | nrg | 110 | U 2 | 7.011 | |
| | | | | | TAT | | | | | | | | | | | | 960 |
| 20 | 305 | Gly | Asp | FILE | Tyr | 310 | Den | ıyı | GIY | GIY | 315 | пув | PHE | AIA | 1111 | 320 | |
| | | | | | GAG Glu | | | | | | | | • | | _ | | 1008 |
| 0.5 | 1111 | Olu | Deu | vai | 325 | 171 | 171 | 1111 | GIII | 330 | GIII | GIY | Vai | neu | 335 | дор | |
| 25 | CGC | GAC | GGC | ACC | ATC | ATC | CAC | CTC | AAG | TAC | CCG | CTG | AAC | TGC | TCC | GAT | 1056 |
| | Arg | Asp | Gly | Thr 340 | Ile | Ile | His | Leu | Lys 345 | Tyr | Pro | Leu | Asn | Cys 350 | Ser | Asp | |
| 30 | | | | _ | AGG | | | | | | | | | | _ | _ | 1104 |
| | Pro | Thr | 355 | GIU | Arg | Trp | ıyr | 360 | GIY | HIS | Met | ser | 365 | GIY | GIN | AIA | |
| 25 | | | | | CAG | | | | | | | | | | | | 1152 |
| 35 | GIU | 370 | Leu | ьец | Gln | AIG | 3 7 5 | GIY | GIU | PIO | irp | 380 | Pne | Leu | Val | AIG | |
| | _ | | | | CAG Gln | | | | | | | | | | | | 1200 |
| 40 | 385 | Del | пси | 561 | GIII | 390 | Gly | nsp | FIIC | vai | 395 | SEL | Val | пец | 261 | 400 | |
| | | | | | GGC | | | | | | | | | | | | 1248 |
| | GIII | PIO | Буъ | Ald | Gly 405 | PIO | Gly | 261 | PIO | 410 | Arg | vai | 1111 | птв | 415 | цуѕ | |
| 45 | GTC | ATG | TGC | GAG | GGT | GGA | CGC | TAC | ACA | GTG | GGT | GGT | TTG | GAG | ACC | TTC | 1296 |
| | Val | Met | Cys | Glu 420 | Gly | Gly | Arg | Tyr | Thr 425 | Val | Gly | Gly | Leu | Glu 430 | Thr | Phe | |
| 50 | | | | | GAC | | | | | | | | | | | | 1344 |
| | Asp | ser | Leu 435 | Tnr | Asp | ьeu | val | Glu 440 | H1S | Pne | гуѕ | гуз | Thr 445 | GIÀ | 116 | GIU | |
| 55 | | | | | GCC Ala | | | | | | | | | | | | 1392 |
| 55 | GIU | 450 | Set | GIY | WIG | FIIE | 455 | TYL | ьец | Arg | GIII | 460 | TÄL | TAL | wrd | IIIL | |

| 5 | 465 | | | | 4 | 70 | 10 0 | JIU | АЅП | Arg | 1 Va. 479 | l Lei 5 | ı Gl | u Le | u As | C AAG n Lys 480 | |
|----|--|-------------------|------------|------------|-------------|-----------|-------------------|------------|------------|-------------------|-----------------|---------------------|--------------|--------------|-----------------------|-----------------------|------|
| | Lys (| Sln (| Slu S | | lu A: 85 | sp T | hr A | la: | AAG Lys | GCT Ala 490 | Gl ⁷ | C TTC / Phe | TG(| G GA | G GA0 1 Gl1 49! | G TTT u Phe 5 | 1488 |
| 10 | GAG A | | 5 | 00 | , 5 0. | | iu v | gT I | 505 | Asn | Leu | His | Gln | 510 | J Lei | ı Glu | 1536 |
| 15 | GGG C | 5 | 15 | | | <u></u> , | 52 | 20 | ıys | Asn | Arg | Tyr | Ьуs 525 | Asn | Ile | Leu | 1584 |
| 20 | CCC TO Pro | 30 | • | | | 53 | 5 | re L | eu (| GIN | Gly | Arg 540 | Asp | Ser | Asn | Ile | 1632 |
| 25 | CCC GC Pro GI 545 | _ | | E -1 | 55 | 0 | 11 MI | .a.A. | sn : | lyr | 11e 555 | Lys | Asn | Gln | Leu | Leu 560 | 1680 |
| | GGC CC | | | 56! | 5 | . шу. | 2 111 | £ 13 | yr 1 5 | 70 | Ala | Ser | Gln | Gly | Cys 575 | Leu | 1728 |
| 30 | GAG GC Glu Al | | 580 |) | . not | , Elle | - 11) | 5 G J | in M 35 | et 1 | Ala | Trp | Gln | Glu 590 | Asn | Ser | 1776 |
| 35 | CGT GT Arg Va | 59 | 5 | | | **** | 600 |) | .u v | aı (| slu . | Lys (| Gly . 605 | Arg | Asn | Lys | 1824 |
| 40 | TGC GTO Cys Val |) | -3- | | 110 | 615 | val | . G1 | у ме | et G | ln A | Arg <i>l</i> 520 | Ala 1 | Tyr | Gly : | Pro | 1872 |
| 45 | TAC TCT Tyr Ser 625 | | | | 630 | Cly | GIU | HI | S AS | sp T 6 | nr 1 35 | Chr G | 3lu 7 | Tyr 1 | Lys 1 | Leu 540 | 1920 |
| 50 | CGT ACC | | | 645 | Jer | 110 | Leu | ASI | 65 65 | n G | ly A | sp L | eu I | le A | rg (| Slu | 1968 |
| 50 | ATC TGG | | 660 | | -12 | Deu | 361 | 665 | Pr | O As | зр Н | is G | ly V 6 | al F 70 | ro S | er | 2016 |
| 55 | GAG CCT Glu Pro | GGG Gly 675 | GGT Gly | GTC Val | CTC Leu | | TTC Phe 680 | CTG Leu | GA As | c cz p Gl | AG A | le A | AC C sn G | AG C ln A | GG C rg G | AG ln | 2064 |

| | | | | CCT Pro | | | | | | _ | _ | | | | _ | _ | 2112 |
|----|--------|-----|-------|-------------|------|------|------|---------|------|-------------|-------------------|------|-------|-----|-----|------|------|
| 5 | | | | | | | | | | | | | | | | | |
| | | | | ACA | | | | | | | | | | | _ | | 2160 |
| | | GIA | Arg | Thr | GIY | | TTE | TTE | vai | ше | 715 | Met | Leu | Met | GIU | 720 | |
| | 705 | | | | | 710 | | | | | 112 | | | | | 120 | |
| 10 | ATC | TCC | ACC | AAG | GGC | CTG | GAC | TGT | GAC | ATT | GAC | ATC | CAG | AAG | ACC | ATC | 2208 |
| | Ile | Ser | Thr | Lys | Gly | Leu | Asp | Cys | Asp | Ile | qaA | Ile | Gln | Lys | Thr | Ile | |
| | | | | | 725 | | | | | 730 | | | | | 735 | | |
| | | | | | | | | | | | | ~~~ | | | | a. a | 2256 |
| 15 | | | | CGG Arg | | | | | | | | | | | | | 2256 |
| 15 | GIII | met | Val | 740 | нта | GIII | ALG | ser | 745 | Mec | vai | GIII | 1111 | 750 | АІА | GIII | |
| | | | | , 10 | | | | | | | | | | | | | |
| | TAC | AAG | TTC | ATC | TAC | GTG | GCC | ATC | GCC | CAG | TTC | ATT | GAA | ACC | ACT | AAG | 2304 |
| | Tyr | Lys | Phe | Ile | Tyr | Val | Ala | Ile | Ala | Gln | Phe | Ile | Glu | Thr | Thr | Lys | |
| 20 | | | 755 | | | | | 760 | | | | | 765 | | | | |
| | አክሮ | አአር | CTC | GAG | cac | CTG | CAG | TCC | CAG | አለር | aac | CNG | GAG | TCG | GAG | TAC | 2352 |
| | | | | Glu | | | | | | | | | | | _ | | 2332 |
| | -1- | 770 | | | | | 775 | | | -1- | | 780 | | | | • | |
| 25 | | | | | | | | | | | | | | | | | |
| | | | | ACC | | | | | | | | | | _ | | _ | 2400 |
| | - | Asn | Ile | Thr | Tyr | | Pro | Ala | Met | Lys | | Ala | His | Ala | Lys | | |
| | 785 | | | | | 790 | | | | | 795 | | | | | 800 | |
| 30 | TCC | CGC | ACC | TCG | TCC | AAA | CAC | AAG | GAG | GAT | GTG | TAT | GAG | AAC | CTG | CAC | 2448 |
| | Ser | Arg | Thr | Ser | Ser | Lys | His | Lys | Glu | Asp | Val | Tyr | Glu | Asn | Leu | His | |
| | | | | | 805 | | | | | 810 | | | | | 815 | | |
| | N COTT | 220 | 220 | 220 | אממ | CAC | CNC | 7 7 7 A | OTTO | ח ח פ | 770 | CAC | ccc. | TON | CCA | GNC | 2496 |
| 35 | | | | AAG Lys | | | | | | | | | | | _ | | 2430 |
| 00 | 1111 | цуз | 7,011 | 820 | 9 | OIU | OIU | 2,5 | 825 | <i></i> , - | <i></i> , <i></i> | 0111 | *** 5 | 830 | | | |
| | | | | | | | | | | | | | | | | | |
| | AAG | GAG | AAG | AGC | AAG | GGT | TCC | CTC | AAG | AGG | AAG | TGA | | | | | 2532 |
| 40 | Lys | Glu | - | Ser | Lys | Gly | Ser | | Lys | Arg | Lys | | | | | | |
| 40 | | | 835 | | | | | 840 | | | | | | | | | |
| • | | | | | | | | | | | | | | | | | |
| | | | (2 |) IN: | FORM | ATIO | N FO | R SE | Q ID | NO: | 117: | | | | | | • |
| | | | | | | | | | | | | | | | | | |
| 45 | | (: | | EQUE | | | | | | | | | | | | | |
| | | | | LENO TYP | | | | | cias | | | | | | | | |
| | | | | STR | | | | | e | | | | | | | | |
| | | | | TOP | | | | _ | | | | | | | | | |
| 50 | | | | | | | | | | | | | | | | | |
| | | | | MOLE | | | - | | | | | | | | | | |
| | | (- | ∨) F. | RAGM | ENT. | LIPE | : ın | cern | al | | | | | | | | |
| | | (: | xi) | SEQU | ENCE | DES | CRIP | TION | : SE | Q ID | NO: | 117: | | | | | |
| 55 | | · | • | | | | | | | | | | | | | | |
| | Met | Val | Ser | Lys | Gly | Glu | Glu | Leu | Phe | Thr | Gly | Val | Val | Pro | Ile | Leu | |
| | | | | | | | | | | | | | | | | | 2 |

| | | | | | | | | | | | | 2 | 18 | | | | | | | • |
|----|----------|----------|---------|------|-------|------------|------------|-------------|----|-----|-------|----------|-----|-----------|----------|------------|------|-----|------|-------------|
| | | | | | | 5 | 5 | | | | | 1 | 0 | | | | | | 15 | |
| | | | | | | | | | | | | | | | | | | | l Se | r Gly |
| 5 | | | | | | | | | | | | | | | | | eu : | Lys | | e Ile |
| | Су | s I 5 | hr 0 | Thi | r Gl | у Lу | s Le | u P 5 | ro | Va: | l Pr | 0 T | 'rp | Pro | Th | 45 r Le | u ' | Val | Th | r Thr |
| | Le 65 | u T | hr | Туг | Gl | y Va | l G1 | n C | ys | Phe | e Se | r A | rg | Туг | 60 Pr | o As | p I | lis | Met | Lys |
| 10 | Gl | n H | is | Asp | Phe | e Ph 85 | | | er | Ala | Me | t P | ro | 75 Glu | ı Gl | у Ту | rī | /al | Glr | 80 1 Glu |
| | | | | | | ∍ Ph | | | | | G1: | 9 7 A | | | | | | | | Glu |
| 15 | | | | | Gli | • | | | ır | Leu | ι Va | • | | | | | - | | | Gly |
| | | | | | | | | p G1 | y. | 120 |) | | | | | | _ | | | Tyr |
| | | | | | | | s As: | n Va | | | | | | | | | | | | Asn |
| 20 | | | | | | Ası | ı Ph | | | | | | | | | | | | | 160 Ser |
| | | | | | Ala | Asp | , | | | | | 1. | ın | | | | | | | |
| 25 | | | al | Leu | | | | | | | | | | | | | | | | Leu |
| 23 | | - Г | s. | | | | | | | | | | | | | | | | | Phe |
| | | | _ | | | | Ile | Th: | | | | | | | 220 | | | | | Ser |
| 30 | | | | | | | 230 Glu | | | | | | | | | | | | | |
| | | | | | | 477 | Ala | | | | | - 7 5 | ^ | | | | | | | |
| 25 | | | r I | Phe | ~ • • | | Arg | | | | 265 | | | | | | | | | |
| 35 | | Se | r i | | | | Gly | | | | | | | | | | | | | |
| | Ser | | - | | | | Asp | 2.7 | 3 | | | | | | 200 | | | | | |
| 40 | | | | | | | 310 Tyr | | | | | | | | | | | | | |
| | | | | | | | Ile | | | | | | | | | | | | | |
| 45 | | | | | | | Trp | | | | | | | | | | | | | |
| 45 | Glu | Thi | : L | | | | | | | | | | | | | | | | | |
| | Glu | | | | | | | ગ /၁ | | | | | | | 200 | | | | | |
| 50 | | | | | | | 330 | | | | | | - 3 | 95 | | | | | | |
| 00 | Gln | | | | | エレコ | | | | | | 4 7 N | ١. | | | | | | le : | Lys |
| | Val | | | | | | | | | - 4 | ュンム | | | | | | | u I | hr i | |
| 55 | Asp | | | | | | | | | | | | | | | | Gl | y I | | |
| | Glu | мıа | Se | er G | TA I | ата | Phe | Val | Ту | r I | Leu . | Arg | G. | ln E | ro | Tyr | ту | r A | la 1 | Chr |

```
450
                          455
                                            460
     Arg Val Asn Ala Ala Asp Ile Glu Asn Arg Val Leu Glu Leu Asn Lys
              470
                              475
     Lys Gln Glu Ser Glu Asp Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe
5
                                    490
                   485
     Glu Ser Leu Gln Lys Gln Glu Val Lys Asn Leu His Gln Arg Leu Glu
               500
                                 505
                                                  510
     Gly Gln Arg Pro Glu Asn Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu
                             520
                                            525
     Pro Phe Asp His Ser Arg Val Ile Leu Gln Gly Arg Asp Ser Asn Ile
10
                         535
     Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu
                           555
           550
     Gly Pro Asp Glu Asn Ala Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu
15
                  565
                                    570
     Glu Ala Thr Val Asn Asp Phe Trp Gln Met Ala Trp Gln Glu Asn Ser
              580 585
     Arg Val Ile Val Met Thr Thr Arg Glu Val Glu Lys Gly Arg Asn Lys
      595
                 600
                                  605
     Cys Val Pro Tyr Trp Pro Glu Val Gly Met Gln Arg Ala Tyr Gly Pro
20
     Tyr Ser Val Thr Asn Cys Gly Glu His Asp Thr Thr Glu Tyr Lys Leu
                   630
                                        635
     Arg Thr Leu Gln Val Ser Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu
25
                                   650
     Ile Trp His Tyr Gln Tyr Leu Ser Trp Pro Asp His Gly Val Pro Ser
               660
                                 665
                                                  670
     Glu Pro Gly Gly Val Leu Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln
                             680
30
     Glu Ser Leu Pro His Ala Gly Pro Ile Ile Val His Cys Ser Ala Gly
                        695
                                           700
     Ile Gly Arg Thr Gly Thr Ile Ile Val Ile Asp Met Leu Met Glu Asn
                     710
                                        715
     Ile Ser Thr Lys Gly Leu Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile
35
                  725 730 735
     Gln Met Val Arg Ala Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln
                                 745
     Tyr Lys Phe Ile Tyr Val Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys
                              760
40
     Lys Lys Leu Glu Val Leu Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr
                          775
                                            780
     Gly Asn Ile Thr Tyr Pro Pro Ala Met Lys Asn Ala His Ala Lys Ala
                      790
                                        795
     Ser Arg Thr Ser Ser Lys His Lys Glu Asp Val Tyr Glu Asn Leu His
45
                   805
                                    810
     Thr Lys Asn Lys Arg Glu Glu Lys Val Lys Lys Gln Arg Ser Ala Asp
               820
                                 825
     Lys Glu Lys Ser Lys Gly Ser Leu Lys Arg Lys
                           840
```

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2562 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

220

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence(B) LOCATION: 1...2559

(D) OTHER INFORMATION:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118

| , , | | | (XI) | SEQ | UENC | E DE | SCRI | PTIO | N: S | EQ I | D NO | :118 | : | | | | |
|-----|-------------------|----------|--------------|-------------------|--------------|--------------|--------------|--------------|--------------|--------------------|--------------|--------------|--------------|-------------|--------------------|------------------|------------|
| 15 | ATO Met | CT Le | G TC u Se | C CG | T GG g Gl | G TG y Tr | G TT p Ph | T CA e Hi | C CG s Ar | A GA g As 10 | C CT p Le | C AG u Se | T GG r Gl | G CT | G GA u As 15 | T GCA p Ala | 48 |
| | | | | 20 | ı Dy | 9 61 | y Ar | 3 GT | y Va. 25 | l Hi | s Gl | y Se: | r Pho | e Lei 30 | ı Al | T CGG a Arg | 96 |
| 20 | | | 35 | <i>-</i> | , 191 | GII | 1 61) | 40 | o Pne | e Sei | : Le | ı Sei | r Va] 45 | l Arg | y Va: | G GGG l Gly | 144 |
| 25 | | 50 | | | | 116 | 55 | 1116 | GIr | n Asr | Ser | 60 Gly | / Asp | Phe | туг | GAC Asp | 192 |
| 30 | 65 | -1- | Cly | Oly | Giu | дуs 70 | Pne | Ala | Thr | Leu | 75 | Glu | Leu | Val | Glu | TAC Tyr 80 | 240 |
| 35 | -1- | | 0111 | . GIII | 85 | GIŸ | vai | ьеи | GIn | Asp 90 | Arg | Asp | Gly | Thr | Ile 95 | ATC Ile | 288 |
| 40 | | | -,0 | TAC Tyr 100 | 110 | neu | ASII | Cys | 105 | Asp | Pro | Thr | Ser | Glu 110 | Arg | Trp | 336 |
| 40 | • | | 115 | CAC His | 1100 | Ser | GIY | 120 | Gin | Ala | Glu | Thr | Leu 125 | Leu | Gln | Ala | 384 |
| 45 | | 130 | 914 | 110 | ııp | 1111 | 135 | Leu | Val | Arg | Glu | Ser 140 | Leu | Ser | Gln | Pro | 432 |
| 50 | GGA Gly 145 | | | var | neu | 150 | vai | ьеи | Ser | Asp | Gln 155 | Pro | Lys | Ala | Gly | Pro 160 | 480 |
| 55 | GGC S | | 0 | | 165 | Vai | Int | HIS | ile | Lys 170 | Val | Met | Cys | Glu | Gly 175 | Gly | 528 |
| | CGC 1 | TAC | ACA | GTG | GGT | GGT | TTG | GAG | ACC | TTC | GAC | AGC | CTC | ACG | GAC | CTG | 576 220 |

| | | | | | | | | | | 221 | | • | | | | | |
|----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-------------------|-----|------|
| | Arg | Tyr | Thr | Val 180 | Gly | Gly | Leu | Glu | Thr 185 | Phe | Asp | Ser | Leu | Thr 190 | Asp | Leu | |
| 5 | | | | | | | | | | | | | | | GCC Ala | | 624 |
| 10 | | | | | | | | | | | | | | | GCT Ala | | 672 |
| | | | | | | | | | | | | | | | GAG Glu | | 720 |
| 15 | | | | | | | | | | | | | | | AAG Lys 255 | | 768 |
| 20 | | | | | | | | | | | | | | | GAG Glu | | 816 |
| 25 | | | | | | | | | | | | | | | AGC Ser | | 864 |
| 30 | | | | | | | | | | | | | | | TAC Tyr | _ | 912 |
| | | | | | | | | | | | | | | | AAC Asn | | 960 |
| 35 | | | | | | | | | | | | | | | AAT Asn 335 | | 1008 |
| 40 | | | | | | | | | | | | | | | ATG Met | | 1056 |
| 45 | | | | | | | | | | | | | | | TGG Trp | | 1104 |
| 50 | | | | | | | | | | | | | | | AAC Asn | | 1152 |
| 55 | | | | | | | | | | | | | | | GTC Val | | 1200 |
| 55 | CCG | CTG | GAC | AAT | GGA | GAC | CTG | ATT | CGG | GAG | ATC | TGG | CAT | TAC | CAG | TAC | 1248 |

| | _ | | | | | | | | | 222 | | | | | | | |
|----|-------------------|-------------------|----------------------|---------------------|-------------------|------------------------|---------------------|-----------------------|-----------------------|-------------------|-------------------|-------------------------------|-------------------|---------------------|-------------------|---------------------|-------------|
| | Pro | o Le | u As | p As | n Gl 40 | y As _l 5 | p Lei | u Ile | e Ar | g Gl: | u Ile O | e Tr | рHi | ѕ Ту | r Gl 41 | n Tyr 5 | |
| 5 | CT(Let | G AG | C TG | G CC p Pro 42 | O AS | C CAT p His | r GG(s Gl) | G GTO | C CCC l Pro 425 | Se: | r GA | G CC | T GG o Gl | G GG y Gl: 43 | y Va | C CTC l Leu | 1296 |
| 10 | AG(Ser | TTO Pho | C CT6 e Les 43 | u Asj | C CAC | G ATO | AAC Asr | C CAC 1 Glr 440 | ı Arc | G CAC | G GA/ | A AG | T CTO | u Pro | r CA | C GCA s Ala | 1344 |
| 15 | GGG Gly | Pro 450 |) TT6 | C ATO | C GT0 ≥ Val | G CAC | C TGC Cys 455 | Ser | GCC Ala | GGC Gly | C ATO | GG(Gl ₃ 46(| Arg | C ACA | A GGG | C ACC | 1392 |
| | ATC Ile 465 | 116 | r GT(≥ Val | C ATO | GAC Asp | ATG Met | Leu | ATG Met | GAG Glu | AAC Asn | ATC Ile 475 | Ser | C ACC | C AAC | GGG Gly | C CTG Leu 480 | 1440 |
| 20 | GAC Asp | TGT Cys | GAC Asp | C ATI | GAC Asp 485 | lle | CAG Gln | AAG Lys | ACC Thr | ATC Ile 490 | Gln | ATC Met | GTC Val | CGG Arg | GCG Ala | G CAG | 1488 |
| 25 | CGC Arg | TCG Ser | GGC | ATG Met | val | CAG Gln | ACG Thr | GAG Glu | GCG Ala 505 | CAG Gln | TAC Tyr | AAG Lys | TTC Phe | ATC Ile 510 | Tyr | GTG Val | 1536 |
| 30 | GCC Ala | ATC | GCC Ala 515 | GIN | TTC Phe | ATT Ile | GAA Glu | ACC Thr 520 | ACT Thr | AAG Lys | AAG Lys | AAG Lys | CTG Leu 525 | GAG Glu | GTC Val | CTG Leu | 1584 |
| 35 | CAG Gln | TCG Ser 530 | CAG Gln | AAG Lys | GGC Gly | CAG Gln | GAG Glu 535 | TCG Ser | GAG Glu | TAC Tyr | GGG Gly | AAC Asn 540 | ATC Ile | ACC Thr | TAT Tyr | CCC Pro | 1632 |
| oo | CCA Pro 545 | GCC Ala | ATG Met | AAG Lys | AAT Asn | GCC Ala 550 | CAT His | GCC Ala | AAG Lys | GCC Ala | TCC Ser 555 | CGC Arg | ACC Thr | TCG Ser | TCC Ser | AAA Lys 560 | 1680 |
| 40 | CAC His | AAG Lys | GAG Glu | GAT Asp | GTG Val 565 | TAT Tyr | GAG Glu | AAC Asn | CTG Leu | CAC His 570 | ACT Thr | AAG Lys | AAC Asn | AAG Lys | AGG Arg 575 | GAG Glu | 1728 |
| 45 | GAG Glu | AAA Lys | GTG Val | AAG Lys 580 | AAG Lys | CAG Gln | CGG Arg | TCA Ser | GCA Ala 585 | GAC Asp | AAG Lys | GAG Glu | AAG Lys | AGC Ser 590 | AAG Lys | GGT Gly | 1776 |
| 50 | TCC Ser | CTC Leu | AAG Lys 595 | AGG Arg | AAG Lys | CGA Arg | Ile | CTG Leu 600 | CAG Gln | TCG Ser | ACG Thr | GTA Val | CCG Pro 605 | CGG Arg | GCC Ala | CGG Arg | 1824 |
| 55 | GAT Asp | CCA Pro 610 | CCG Pro | GTC Val | GCC Ala | Inr | ATG Met 615 | GTG Val | AGC Ser | AAG Lys | Gly | GAG Glu 620 | GAG Glu | CTG Leu | TTC Phe | ACC Thr | 1872 |
| | GGG (| GTG | GTG | ccc | ATC | CTG | GTC (| GAG · | CTG (| GAC (| GGC | GAC | GTA | AAC | GGC | CAC | 1920 222 |

| | | | | | | | | | | 223 | | | | | | | |
|----|------------|-----|------------|-----|-----|------------|-----|-----|-----|-----|------------|-------------------|-----|-----|-----|------------|------------|
| | Gly 625 | Val | Val | Pro | Ile | Leu 630 | Val | Glu | Leu | Asp | Gly 635 | Asp | Val | Asn | Gly | His 640 | |
| 5 | | | | | | | | | | | | GCC Ala | | | | | 1968 |
| 10 | | | | | | | | | | | | CTG Leu | | | | | 2016 |
| | | | Leu | GTG | | | | Thr | TAC | | | CAG Gln | Cys | TTC | | | 2064 |
| 15 | | | | | | | | | | | | AAG Lys | | | | | 2112 |
| 20 | | | | | | | | | | | | 700 AAG | | | | | 2160 |
| | 705 | • | • | | | 710 | _ | | | | 715 | Lys | • | • | | 720 | 2208 |
| 25 | - | - | | | 725 | | | - | | 730 | - | Asp | | | 735 | | |
| 30 | | | | | | | | | | | | GAC Asp | | | | | 2256 |
| | | | | | | | | | | | | AAC Asn | | | | | 2304 |
| 35 | | | | | | | | | | | | TTC Phe 780 | | | | | 2352 |
| 40 | | | | | | | | | | | | CAC His | | | | | 2400 |
| 45 | | | | | | | | | | | | GAC Asp | | | | | 2448 |
| 50 | | | | | | | | | | | | GAG Glu | | | | | 2496 |
| | | | Leu | | | | | Thr | | | | ATC Ile | | | | | 2544 |
| 55 | GAC | GAG | 835 CTG | TAC | AAG | TAA | | 840 | | | | | 043 | | | | 2562 22 |

224

Asp Glu Leu Tyr Lys

45

```
850
  5
                (2) INFORMATION FOR SEQ ID NO:119:
             (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 853 amino acids
               (B) TYPE: amino acid
 10
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
             (ii) MOLECULE TYPE: protein
             (v) FRAGMENT TYPE: internal
 15
             (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:
      Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
                                          10
20
      Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
                 20
                                     2.5
      Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
                                40
      Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
25
      Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
                         70
                                              75
      Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
                    85
                                         90
      His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
30
                 100
                                    105
      Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
                                 120
                                           125
      Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
35
                           135
                                                 140
      Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
                       150
                                            155
     Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                     165
                                         170
     Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
40
                180
```

185 Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe 195 200 205 Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp 215 220 Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp 230 235 Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln 245 250

Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn 50 260 265 Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg

280 285 Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile

55 295 300 Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

| | | | | | | | | | | LLO | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------------|
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| | Lys | Thr | Tyr | Ile | Ala 325 | Ser | Gln | Gly | Cys | Leu 330 | Glu | Ala | Thr | Val | Asn 335 | Asp |
| 5 | Phe | Trp | Gln | Met 340 | Ala | Trp | Gln | Glu | Asn 345 | | Arg | Val | Ile | Val 350 | Met | Thr |
| | Thr | Arg | Glu 355 | | Glu | Lys | Gly | Arg 360 | | Lys | Cys | Val | Pro 365 | | Trp | Pro |
| | Glu | Val | Gly | Met | Gln | Arg | Ala 375 | | Gly | Pro | Tyr | | | Thr | Asn | Сув |
| 10 | _ | | His | Asp | Thr | | | Tyr | Lys | Leu | _ | 380 Thr | Leu | Gln | Val | |
| | 385 Pro | Leu | Asp | Asn | | 390 Asp | Leu | Ile | Arg | | 395 Ile | Trp | His | Tyr | | 400 Tyr |
| | Levi | C0* | Trp | Dro | 405 | u; c | Gly. | Ma I | Dro | 410 | <i>c</i> 1 | Dro | <i>α</i> 1 | C1** | 415 | Ton |
| 15 | | | _ | 420 | | | | | 425 | | | | _ | 430 | | |
| | | | Leu 435 | _ | | | | 440 | _ | | | | 445 | | | |
| 00 | | 450 | Ile | | | | 455 | | | | | 460 | | | | |
| 20 | 465 | | Val | | _ | 470 | | | | | 475 | | | - | _ | 480 |
| | | | Asp | | 485 | | | - | | 490 | | | | _ | 495 | |
| 25 | | | Gly | 500 | | | | | 505 | | - | _ | | 510 | _ | |
| | | | Ala 515 | | | | | 520 | | | - | | 525 | | | |
| | | 530 | Gln | _ | | | 535 | | | _ | _ | 540 | | | _ | |
| 30 | Pro 545 | Ala | Met | Lys | Asn | Ala 550 | His | Ala | Lys | Ala | Ser 555 | Arg | Thr | Ser | Ser | Ъуз 560 |
| | | | Glu | _ | 565 | _ | | | | 570 | | _ | | _ | 575 | |
| 35 | | | Val | 580 | _ | | _ | | 585 | _ | _ | | _ | 590 | _ | _ |
| | | | Lys 595 | | _ | | | 600 | | | | | 605 | _ | | _ |
| | | 610 | Pro | | | | 615 | | | | | 620 | | | | |
| 40 | 625 | | Val | | | 630 | | | | - | 635 | - | | | - | 640 |
| | Lys | Phe | Ser | Val | Ser 645 | Gly | Glu | Gly | Glu | Gly 650 | Asp | Ala | Thr | Tyr | Gly 655 | Lys |
| 45 | Leu | Thr | Leu | Lys 660 | Phe | Ile | Cys | Thr | Thr 665 | Gly | Lys | Leu | Pro | Val 670 | Pro | Trp |
| | Pro | Thr | Leu 675 | Val | Thr | Thr | Leu | Thr 680 | Tyr | Gly | Val | Gln | Cys 685 | Phe | Ser | Arg |
| | Tyr | Pro 690 | Asp | His | Met | Lys | Gln 695 | His | Asp | Phe | Phe | Lys 700 | Ser | Ala | Met | Pro |
| 50 | 705 | _ | Tyr | | | 710 | _ | | | | 715 | _ | _ | _ | _ | 720 |
| | Tyr | Lys | Thr | Arg | Ala 725 | Glu | Val | Lys | Phe | Glu 730 | Gly | Asp | Thr | Leu | Val 735 | Asn |
| 55 | Arg | Ile | Glu | Leu 740 | Lys | Gly | Ile | Asp | Phe 745 | Lys | Glu | Asp | Gly | Asn 750 | Ile | Leu |
| | Gly | His | Lys | Leu | Glu | Tyr | Asn | Tyr | Asn | Ser | His | Asn | Val | Tyr | Ile | Met |

| | 226 | • |
|----|--|----------------------|
| | 755 760 765 | |
| | Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile As | |
| _ | Asn Ile Glu Asp Gly Ser Val Gly Ley Ale Ass | lm 3 |
| 5 | | |
| | Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Ty | /r Leu |
| | Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg As | l5 sp His |
| 10 | Met Val Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gl | |
| | Asp Glu Leu Tyr Lys 850 | |
| 15 | (2) INFORMATION FOR SEQ ID NO:120: | |
| 20 | (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2994 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear | |
| 25 | (ii) MOLECULE TYPE: cDNA (ix) FEATURE: | |
| | (A) NAME/KEY: Coding Sequence(B) LOCATION: 12991(D) OTHER INFORMATION: | |
| 30 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120: | |
| 35 | ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile 1 5 10 15 | CTG 48 |
| 33 | GTC GAG CTG GAC GGC GAC GTA AAC GGG GAG AAC | |
| | Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser 20 25 30 | GGC 96 Gly |
| 40 | GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC | 1 ma |
| | Glu Gly Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe 35 40 45 | Ile 144 |
| 45 | TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr | ACC 192 |
| | 50 55 60 | Inr |
| | CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG | AAC 240 |
| 50 | Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met 70 75 | AAG 240 Lys 80 |
| 55 | CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln 85 90 95 | Glu |
| | CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC | GAG 336 226 |

| | | | | | | | | | | 227 | | | | | | | | |
|----|-----|-----|-----|------------|-----|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|------|----|
| | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | Asn | Tyr | Lys | Thr | Arg 110 | Ala | Glu | | |
| 5 | | | | | | GAC Asp | | | | | | | | | | _ | 384 | |
| 10 | | | | | | GAC Asp | | | | | | | | | _ | | 432 | |
| | | | | | | AAC Asn 150 | | | | | | | | | | | 480 | |
| 15 | | | | | | TTC Phe | | | | | | _ | | | _ | | 528 | |
| 20 | | | | | | CAC His | | | | | | | | | | | 576 | |
| 25 | | | | | | GAC Asp | | | | | | | _ | | _ | | 624 | |
| 30 | | | | | | GAG Glu | | | | | | | | | | | 672 | |
| 25 | | | | | | ATC Ile 230 | | | | | | | | | | | 720 | |
| 35 | | | | | | GCT Ala | | | | | | | | | | | 768 | |
| 40 | | | | | | GGC Gly | | | | | | | | | _ | | 816 | |
| 45 | - | | | | | TTC Phe | - | | _ | | | | | _ | | _ | 864 | |
| 50 | | | | | | GCA Ala | | | | | | | | | | | 912 | |
| | | | | | | TGG Trp 310 | | | | | | | | | | | 960 | |
| 55 | AAC | CAT | GCC | AAT | GTT | GTA | AAG | GCC | TGT | GAT | GTT | CCT | GAA | GAA | TTG | AAT | 1008 | 22 |

| | | | | | | | | | | 228 | | | | | | | |
|----|-------------------|--------------------|-----------------------------------|-----------------------|-----------------------|-----------------------|--------------------|---------------------|-------------------|-------------------|----------------------------|--------------------|--------------------|-------------------|-------------------|-----------------------|-------------|
| | | | | | | | | | | 33 | 0 | | | | 33 | eu Asn 35 | |
| 5 | | | | 34 | 10 | p va | I PI | o re | u Le 34 | u A1 5 | a Me | t Gl | u Ty | r Cy 35 | s Se 0 | CT GGA er Gly | • |
| 10 | GG Gl | A GA y As | AT CT sp Le 35 | | A AA | G CTO | G CT u Le | C AA u As: 36 | п гу | A CC s Pr | A GA o Gl | A AA u As | T TG n Cy 36 | s Cy | T GG s Gl | A CTT y Leu | 1104 |
| 15 | AA. Ly: | A GA S G1 37 | | GC CA | G AT | A CT' | TC 1 Se: 37! | r net | A CT/ | A AG | T GA' r As _l | T AT p Il 38 | e Gl | G TC' Y Se: | T GG r Gl | G ATT y Ile | 1152 |
| | CG/ Arg 385 | A TA J Ty | T TT | G CA u Hi | T GA | A AAC 1 Asr 390 | ı uy: | A ATT | Γ ATA ≥ Ile | A CA | CGA Arg 395 | j As | T CT! p Lei | A AAI 1 Lys | A CC | T GAA O Glu 400 | 1200 |
| 20 | AAC Asn | AT. | A GT e Va | T CT | T CAC u Glr 405 | , web | ' GTT | GGT Gly | GGA Gly | AAC Lys | Il€ | A ATA | A CAT | AAA Lys | A AT | A ATT | 1248 |
| 25 | GAT Asp | CT(| G GG u Gl | A TAT Y Ty: 420 | . MIG | AAA Lys | GAT Asp | GTT Val | GAT Asp 425 | GIn | GGA Gly | AGT Ser | CTG | TGT Cys | Thi | A TCT | 1296 |
| 30 | TTT Phe | GT(| G GG/ 1 Gl ₃ 435 | | CTG | CAG Gln | TAT Tyr | CTG Leu 440 | GCC Ala | CCA Pro | GAG Glu | CTC | TTT Phe | GAG Glu | AAT Asr | AAG Lys | 1344 |
| 35 | CCT Pro | TAC Tyr 450 | | GCC Ala | ACT Thr | GTT Val | GAT Asp 455 | TAT Tyr | TGG Trp | AGC Ser | TTT Phe | GGG Gly 460 | Thr | ATG Met | GTA Val | TTT | 1392 |
| | GAA Glu 465 | TGT Cys | 'ATT | GCT Ala | GGA Gly | TAT Tyr 470 | AGG Arg | CCT Pro | TTT Phe | TTG Leu | CAT His | CAT His | CTG Leu | CAG Gln | CCA Pro | TTT Phe 480 | 1440 |
| 40 | ACC Thr | TGG Trp | CAT His | GAG Glu | AAG Lys 485 | ATT Ile | AAG Lys | AAG Lys | AAG Lys | GAT Asp 490 | CCA Pro | AAG Lys | TGT Cys | ATA Ile | TTT Phe 495 | | 1488 |
| 45 | TGT Cys | GAA Glu | GAG Glu | ATG Met 500 | TCA Ser | GGA Gly | GAA Glu | vai | CGG Arg 505 | TTT Phe | AGT Ser | AGC Ser | CAT His | TTA Leu 510 | | CAA Gln | 1536 |
| 50 | CCA Pro | AAT Asn | AGC Ser 515 | CTT Leu | TGT Cys | AGT Ser | Leu | ATA Ile 520 | GTA Val | GAA Glu | CCC Pro | ATG Met | GAA Glu 525 | AAC Asn | TGG Trp | CTA Leu | 1584 |
| 55 | CAG Gln | TTG Leu 530 | ATG Met | TTG Leu | AAT Asn | TTD A | GAC Asp 535 | CCT Pro | CAG (| CAG Gln | Arg | GGA Gly 540 | GGA Gly | CCT Pro | GTT Val | GAC Asp | 1632 |
| 00 | CTT | ACT | TTG | AAG | CAG | CCA 1 | AGA ' | TGT : | TTT (| GTA ' | | | GAT (| CAC . | ATT | TTG | 1680 228 |

| | | | | | | | | | | 229 | | | | | | | |
|----|------------|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|------|
| | Leu 545 | Thr | Leu | Lys | Gln | Pro 550 | Arg | Cys | Phe | Val | Leu 555 | Met | Asp | His | Ile | Leu 560 | |
| 5 | | | | | | CAC His | _ | | | | | | _ | | _ | _ | 1728 |
| 10 | | | | | | CCT Pro | | | | | | | | _ | | | 1776 |
| 15 | | | | | | GGA Gly | | | | | | | | | | | 1824 |
| | | | | | | CTG Leu | | | | | | | | _ | | _ | 1872 |
| 20 | | | | | | GGC Gly 630 | | | | | | - | | | | | 1920 |
| 25 | | | | | | TAT Tyr | | | | | | | | | | | 1968 |
| 30 | - | | | | | ATT Ile | | | | | | | | | | | 2016 |
| 35 | | | | | | GTG Val | | | | | | | | | | _ | 2064 |
| 33 | | | | | | AGC Ser | | | | | | | | | _ | | 2112 |
| 40 | | | | | | TAT Tyr 710 | | | | | | | | | | | 2160 |
| 45 | | | | | | CAA Gln | | | | | | | | | | | 2208 |
| 50 | | | | | | GAC Asp | | | | | | | | | | | 2256 |
| EE | | | | | | AAA Lys | | | | | | | | | | | 2304 |
| 55 | AAG | GCC | ATC | CAC | TAT | GCT | GAG | GTT | GGT | GTC | ATT | GGA | TAC | CTG | GAG | GAT | 2352 |

| | | | | | | | | | | 200 | | | | | | | |
|----|-------------------|-------------------|----------------------|-----------------------|-----------------------|-----------------------|-------------------|-------------------|-----------------------|---------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------|
| | Lу | s Al 77 | a I] '0 | e Hi | ѕ Ту | r Ala | a Gli 77! | u Va 5 | l Gl | y Va | 1 11 | e Gl 78 | | r Le | u Gl | u Asp | |
| 5 | CA: Gl: 78! | | T AI e Me | TG TC | T TT r Le | G CAT u His 790 | AT & | r ga a Gl | A AT u Il | C AT e Me | G GG t G1 79 | y Le | A CAG | G AA n Ly | G AG s Se | C CCC r Pro 800 | 2400 |
| 10 | TA: | r GG | A AG y Ar | A CG | T CAG g Gl: 80! | п Сту | GAC Asp | TTO Le | G ATO | G GA t Gl: 81 | u Se: | r CTO | G GA/ | A CAG | G CG n Ar | T GCC g Ala 5 | 2448 |
| 15 | AT7 Ile | GA' | T CT | A TA' u Ty: 820 | г гу | G CAG S Gln | TTA Leu | AA Ly: | A CAG S His 825 | s Arg | A CC | r TC# | A GAT | CAC His | s Se | C TAC r Tyr | 2496 |
| | AGT Ser | GA(| 2 AG 5 Se: 83! | | A GAO | ATG | GTG Val | AA/ Lys 840 | 3 116 | ATT | GTC Val | G CAC | ACT Thr | · Va] | G CAC | G AGT | 2544 |
| 20 | CAG Gln | GAC Asp 850 | , vr. | r GTC g Val | CTC Leu | AAG Lys | GAG Glu 855 | CTC | TTT Phe | GGT Gly | CAT His | TTG Leu 860 | Ser | AAC Lys | TTC Lev | TTG | 2592 |
| 25 | GGC Gly 865 | TG1 Cys | C AAC | G CAG | AAG Lys | ATT Ile 870 | ATT Ile | GAT Asp | CTA | CTC Leu | CCT Pro 875 | Lys | GTG Val | GAA Glu | GTG Val | GCC Ala 880 | 2640 |
| 30 | CTC Leu | AGT Ser | ' AA'I ' Asn | ATC | AAA Lys 885 | GAA Glu | GCT Ala | GAC Asp | AAT Asn | ACT Thr 890 | GTC Val | ATG Met | TTC Phe | ATG Met | CAG Gln 895 | Gly | 2688 |
| 35 | AAA Lys | AGG Arg | CAG Gln | AAA Lys 900 | GAA Glu | ATA Ile | TGG Trp | CAT His | CTC Leu 905 | CTT Leu | AAA Lys | ATT Ile | GCC Ala | TGT Cys 910 | ACA Thr | CAG Gln | 2736 |
| | AGT Ser | TCT Ser | GCC Ala 915 | CGC Arg | TCT Ser | CTT Leu | GTA Val | GGA Gly 920 | TCC Ser | AGT Ser | CTA Leu | GAA Glu | GGT Gly 925 | GCA Ala | GTA Val | ACC Thr | 2784 |
| 40 | CCT Pro | CAG Gln 930 | ACA Thr | TCA Ser | GCA Ala | TGG Trp | CTG Leu 935 | CCC Pro | CCG Pro | ACT Thr | TCA Ser | GCA Ala 940 | GAA Glu | CAT His | GAT Asp | CAT His | 2832 |
| 45 | TCT Sér 945 | CTG Leu | TCA Ser | TGT Cys | GTG Val | GTA / Val / 950 | ACT Thr | CCT Pro | CAA Gln | GAT Asp | GGG Gly 955 | GAG Glu | ACT Thr | TCA Ser | GCA Ala | CAA Gln 960 | 2880 |
| 50 | ATG Met | ATA Ile | GAA Glu | GAA Glu | AAT Asn 965 | TTG A | AAC (Asn (| TGC Cys | CTT Leu | GGC Gly 970 | CAT His | TTA Leu | AGC Ser | ACT Thr | ATT Ile 975 | ATT Ile | 2928 |
| 55 | CAT (| GAG Glu | GCA Ala | AAT Asn 980 | GAG Glu | GAA (Glu (| CAG (Gln (| GGC Gly | AAT Asn 985 | AGT Ser | ATG Met | ATG . Met . | Asn : | CTT Leu 990 | GAT Asp | TGG Trp | 2976 |
| - | AGT T | rgg | TTA | ACA | GAA ' | TGA | | | | | | | | | | | 2994 230 |

231

Ser Trp Leu Thr Glu 995

5 (2) INFORMATION FOR SEQ ID NO:121:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 997 amino acids
 - (B) TYPE: amino acid
- (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

| | Met 1 | Val | Ser | Lys | Gly 5 | Glu | Glu | Leu | Phe | Thr 10 | Gly | Val | Val | Pro | Ile 15 | Leu |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 20 | Val | Glu | Leu | Asp 20 | Gly | Asp | Val | Asn | Gly 25 | His | Lys | Phe | Ser | Val 30 | Ser | Gly |
| | Glu | Gly | Glu 35 | Gly | Asp | Ala | Thr | Tyr 40 | Gly | Lys | Leu | Thr | Leu 45 | Lys | Phe | Ile |
| 25 | _ | Thr 50 | | _ | - | | 55 | | | - | | 60 | | | | |
| | 65 | Thr | | | | 70 | | | | | 75 | | | | | 80 |
| | Gln | His | Asp | Phe | Phe 85 | Lys | Ser | Ala | Met | Pro 90 | Glu | Gly | Tyr | Val | Gln 95 | Glu |
| 30 | Arg | Thr | Ile | Phe 100 | Phe | Lys | Asp | Asp | Gly 105 | Asn | Tyr | Lys | Thr | Arg 110 | Ala | Glu |
| | Val | Lys | Phe 115 | Glu | Gly | Asp | Thr | Leu 120 | Val | Asn | Arg | Ile | Glu 125 | Leu | Lys | Gly |
| 35 | Ile | Asp 130 | Phe | Lys | Glu | Asp | Gly 135 | Asn | Ile | Leu | Gly | His 140 | Lys | Leu | Glu | Tyr |
| | Asn 145 | Tyr | Asn | Ser | His | Asn 150 | Val | Tyr | Ile | Met | Ala 155 | Asp | Lys | Gln | Lys | Asn 160 |
| | | Ile | _ | | 165 | | <u>.</u> | | | 170 | | | | _ | 175 | |
| 40 | Val | Gln | Leu | Ala 180 | Asp | His | Tyr | Gln | Gln 185 | Asn | Thr | Pro | Ile | Gly 190 | qaA | Gly |
| | Pro | Val | Leu 195 | Leu | Pro | Asp | Asn | His 200 | Tyr | Leu | Ser | Thr | Gln 205 | Ser | Ala | Leu |
| 45 | Ser | Lys 210 | Asp | Pro | Asn | Glu | Lys 215 | Arg | Asp | His | Met | Val 220 | Leu | Leu | Glu | Phe |
| | Val 225 | Thr | Ala | Ala | Gly | 11e 230 | Thr | Leu | Gly | Met | Asp 235 | | Leu | Tyr | Lys | Ser 240 |
| | Gly | Leu | Arg | Ser | Arg 245 | Ala | Gln | Ala | Ser | Asn 250 | Ser | Thr | Met | Glu | Arg 255 | Pro |
| 50 | Pro | Gly | Leu | Arg 260 | Pro | Gly | Ala | Gly | Gly 265 | Pro | Trp | Glu | Met | Arg 270 | Glu | Arg |
| | | Gly | 275 | - | - | | - | 280 | | - | | • | 285 | | | |
| 55 | Leu | Asp 290 | Leu | Lys | Ile | Ala | Ile 295 | Lys | Ser | Cys | Arg | Leu 300 | Glu | Leu | Ser | Thr |
| | T | 7 | 7 | 07 | 70 | (T) | G | TT - | ~1· | T] _ | C1 ~ | T1- | B4 ~ - | T | 7 | T 011 |

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

| | | | | | | | | | | | 2 | 32 | | | | | | | |
|----|------------|------------|-------------|-------------|------|------------|------------|------------|----------|------------|------|-------|------------|----------|------------|-----------|-----------|------------|--------------|
| | 3 (| | | | | : | 310 | | | | | | 31 | 5 | | | | | 320 |
| | | | | | J | 23 | | | | | | 3 7 N | Va | l Pr | | | | | u Asn |
| 5 | | | | | | | | | | 4.4 | eu 2 | Ala | Me | | | _ | | | r Gly |
| | G1 | y As | sp Le 3! | eu Ai 55 | g L | ys I | eu 1 | Leu | As 36 | n Ly | /S] | Pro | Gli | ı As | | s C | 50 'ys | Gly | / Leu |
| | Ly | 's G] | lu Se 70 | er Gl | ln I | le I | eu s | Ser 375 | Le | u Le | eu s | Ser | Ası |) Il | 36 e Gl | 5 .y S | er | Gly | / Ile |
| 10 | Ar 38 | g Ту 5 | r Le | eu Hi | s G | lu A | sn I 90 | уys | 11 | e I1 | e F | lis | Arg | 38 As | p Le | u L | ys | Pro | Glu |
| | As | n Il | e Va | al Le | u G: | ln A 05 | sp V | /al | Gl | y Gl | у І | ys | 399 Ile | ll | e Hi | s L | ys | Ile | 400 : Ile |
| 15 | As | p Le | u Gl | у Ту 42 | r Al | la L | ys A | sp | Va: | l As | рG | ln | Gly | se: | r Le | | | 415 Thr | Ser |
| | Pho | e Va | 1 G1 43 | y Th | | eu G | ln I | уr | Le: | 42 1 Al | a P | ro | Glu | Le | | e G | 30 lu | Asn | Lys |
| | Pro | о Ту 45 | r Th O | r Al | a Th | r V | al A | sp 55 | Ту | Tr | p S | er | Phe | Gly | 44. Th: | 5 r Me | et | Val | Phe |
| 20 | | _ | | e Al | | | /r A 70 | rg | | | | | 4 7 F | | Le | | | | |
| | | | | s Gl | | s I. | le L | | | | | | | | | | | | |
| 25 | | | | u Mei 50 | • | | | | | 501 | g Pi | he | | | | | eu - | | |
| | | | | | | | | | ヘノロ | Va. | l G | | | | | | n ' | | |
| | | | | t Leu | | | | | | | | | | | Gly | ' Pr | | | |
| 30 | | | | ı Lys | | JJ | v | | | | | | | Met | Asp | | | | |
| | | | | ; Il∈ | | | | | | | | t | Thr | | | | | | |
| 35 | | | | Leu 580 | | | | | | | Le | u : | | | | | n S | Ser | |
| | | | | | | | | | nuu | | | | | | | Le | u I | | |
| 40 | | | | Ile | | | | | | | | | | | Ser | | | | |
| 40 | | | | Val | | | | | | | | | | | | | | | |
| | | | | Thr | | | | | | | | | | | | | | eu | Ser |
| 45 | | | | Asn 660 | | | | | | | | | | | | | ı P | ro | |
| | | | | Arg | | | | | | | | | | | | | | | |
| 50 | | | | Asp | | | | | | | | | | | | | | | |
| | | | | Leu | | | | | | | | | | | | | | | |
| | | | | Ala | | | | | | | | | | | | | | | |
| 55 | Lys Glv | | | | | | | | | | | | | | | | | | |
| | Gly | -10 | 261 | SET | oru | гÀв | мet | L | eu : | Lys | Ala | T | rp I | yys | Glu | Met | G] | u G | lu |

| | | | 755 | | | | | 760 | | | | | 765 | | | | |
|----|-----|------------|-----------|------------|--------|-------|----------------|------------|------------|------|-------|------------|-----|------------|------------|------------|----|
| | Lys | Ala | | His | Tyr | Ala | Glu | | Gly | Val | Ile | Gly | | Leu | Glu | Asp | |
| | | 770 | | | | | 775 | | | | | 780 | | | | _ | |
| 5 | 785 | 11e | Met | Ser | Leu | H15 | Ala | GIu | He | Met | 795 | Leu | GIn | Lys | Ser | Pro 800 | |
| Ū | | Gly | Arg | Arg | Gln | | Asp | Leu | Met | Glu | | Leu | Glu | Gln | Arg | | |
| | _ | _ | _ | _ | 805 | _ | - | | | 810 | | | | | 815 | | |
| | Ile | Asp | Leu | - | Lys | Gln | Leu | Lys | | Arg | Pro | Ser | Asp | | Ser | Tyr | |
| 10 | Ser | Asp | Ser | 820 Thr | Glu | Met | Val | Lvs | 825 Ile | Ile | Val | His | Thr | 830 Val | Gln | Ser | |
| | | | 835 | | | | | 840 | | | | | 845 | | | | |
| | Gln | | Arg | Val | Leu | Lys | | Leu | Phe | Gly | His | | | Lys | Leu | Leu | |
| | Glv | 850 Cve | Lve | Gln | Lve | Tle | 855 | Δen | I.em | T.em | Pro | 860 | | Glu | Val | בות | |
| 15 | 865 | CyS | _ | Q.1.1. | БуБ | 870 | 110 | Asp | Deu | ncu | 875 | БуБ | VOI | GIU | Val | 880 | |
| | Leu | Ser | Asn | Ile | Lys | Glu | Ala | Asp | Asn | Thr | Val | Met | Phe | Met | Gln | Gly | |
| | | | 03 | • | 885 | T3 - | | *** | • | 890 | • | -7- | | a | 895 | a 1 | |
| | гув | Arg | GIN | 900 | GIU | 11e | Trp | HIS | ьец 905 | Leu | гÀг | iie | Ala | 910 | Thr | Gin | |
| 20 | Ser | Ser | Ala | | Ser | Leu | Val | Gly | | Ser | Leu | Glu | Gly | | Val | Thr | |
| | | | 915 | | | | | 920 | | | | | 925 | | | | |
| | Pro | Gln 930 | Thr | Ser | Ala | Trp | Leu 935 | Pro | Pro | Thr | Ser | Ala 940 | Glu | His | Asp | His | |
| | Ser | | Ser | Cys | Val | Val | | Pro | Gln | Asp | Glv | | Thr | Ser | Ala | Gln | |
| 25 | 945 | | | | | 950 | | | | _ | 955 | | | | | 960 | |
| | Met | Ile | Glu | Glu | | Leu | Asn | Cys | Leu | _ | His | Leu | Ser | Thr | Ile | Ile | |
| | *** | ~1 | n 7 - | 7 ~~ | 965 | G1 | ~1 ~ | ~ 2 | D | 970 | Mah | M-4- | n | T | 975 | (Trees | |
| | HIS | GIU | Ald | 980 | GIU | Giu | GIII | GIY | 985 | ser | Mec | Met | ASI | 990 | Asp | 11p | |
| 30 | ser | Trp | Leu | | Glu | | | | | | | | | | | | |
| | | | 995 | | | | | | | | | | | | | | |
| | | | (2) | TNI | ORMA | OTTL | I FOI | SEC | מד כ | NO: | 122 · | | | | | | |
| | | | (2) | | OILL I | | | 023, | 2 10 | | | | | | | | |
| 35 | | (: | | | | | CTE | | | | | | | | | | |
| | | | | | | | l bas ic ac | _ | airs | | | | | | | | |
| | | | | | | | G: si | | 9 | | | | | | | | |
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| 40 | | | | | | | _ | | | | | | | | | | |
| | | | | OLEC | | TYPE | E: cI | ANC | | | | | | | | | |
| | | (- | LA, 1 | LAIC | Mr. | | | | | | | | | | | | |
| | | | | | | | Codin | _ | _ | nce | | | | | | | |
| 45 | | | | | | | 12 | | | | | | | | | | |
| | | | (U) | 011 | ier . | LNFOR | RMAT | LON: | | | | | | | | | |
| | | () | ci) S | EQUI | ENCE | DESC | CRIP | rion | : SE | Q ID | NO: | 122: | | | | | |
| F0 | | | | | | | | | | | | | | | | | |
| 50 | | | | | | | | | | | | | | | TGG Trp | | 48 |
| | 1 | JIU | ALY | -10 | 5 | GLY | Leu | vra | 7.0 | 10 | VIG | GIY | GIY | -10 | 11p | JIU | |
| | | | | | | | | | | | | | | | | | |
| 66 | | | | | | | | | | | | | | | CTG | | 96 |
| 55 | Mec | Arg | GIII | Arg | neu | GIÀ | Inr | GIA | G1y 25 | rne | чτλ | ASN | val | Cys 30 | Leu | Tyr | |
| | | | | | | | | | | | | | | | | | |

| F | CAG Gln | CAT His | CGG Arg 35 | GAA Glu | CTT Leu | GAT Asp | CTC Leu | AAA Lys 40 | ATA Ile | GCA Ala | ATT | AAG Lys | TCT Ser 45 | TGT Cys | CGC Arg | CTA Leu | 144 |
|----|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----|
| 5 | GAG Glu | CTA Leu 50 | AGT Ser | ACC Thr | AAA Lys | AAC Asn | AGA Arg 55 | GAA Glu | CGA Arg | TGG Trp | TGC Cys | CAT His 60 | GAA Glu | ATC Ile | CAG Gln | ATT Ile | 192 |
| 10 | ATG Met 65 | AAG Lys | AAG Lys | TTG Leu | AAC Asn | CAT His 70 | GCC Ala | AAT Asn | GTT Val | GTA Val | AAG Lys 75 | GCC Ala | TGT Cys | GAT Asp | GTT Val | CCT Pro 80 | 240 |
| 15 | GAA Glu | GAA Glu | TTG Leu | AAT Asn | ATT Ile 85 | TTG Leu | ATT Ile | CAT | GAT Asp | GTG Val 90 | CCT Pro | CTT Leu | CTA Leu | GCA Ala | ATG Met 95 | GAA Glu | 288 |
| 20 | Tyr | Cys | TCT Ser | Gly 100 | Gly | Asp | Leu | Arg | Lys 105 | Leu | Leu | Asn | Lys | Pro 110 | Glu | Asn | 336 |
| 25 | TG T Cys | TGT Cys | GGA Gly 115 | CTT Leu | AAA Lys | GAA Glu | AGC Ser | CAG Gln 120 | ATA Ile | CTT Leu | TCT Ser | TTA Leu | CTA Leu 125 | AGT Ser | GAT Asp | ATA Ile | 384 |
| | GGG Gly | TCT Ser 130 | GGG Gly | ATT Ile | CGA Arg | TAT Tyr | TTG Leu 135 | CAT His | GAA Glu | AAC Asn | AAA Lys | ATT Ile 140 | ATA Ile | CAT His | CGA Arg | GAT Asp | 432 |
| 30 | CTA Leu 145 | AAA Lys | CCT Pro | GAA Glu | AAC Asn | ATA Ile 150 | GTT Val | CTT Leu | CAG Gln | GAT Asp | GTT Val 155 | GGT Gly | GGA Gly | AAG Lys | ATA Ile | ATA Ile 160 | 480 |
| 35 | CAT His | AAA Lys | ATA Ile | ATT Ile | GAT Asp 165 | CTG Leu | GGA Gly | TAT Tyr | GCC Ala | AAA Lys 170 | GAT Asp | GTT Val | GAT Asp | CAA Gln | GGA Gly 175 | AGT Ser | 528 |
| 40 | CTG Leu | TGT Cys | ACA Thr | TCT Ser 180 | TTT Phe | GTG Val | GGA Gly | ACA Thr | CTG Leu 185 | CAG Gln | TAT Tyr | CTG Leu | GCC Ala | CCA Pro 190 | GAG Glu | CTC Leu | 576 |
| 45 | TTT Phe | GAG Glu | AAT Asn 195 | AAG Lys | CCT Pro | TAC Tyr | Thr | GCC Ala 200 | ACT Thr | GTT Val | GAT Asp | TAT Tyr | TGG Trp 205 | AGC Ser | TTT Phe | gly ggg | 624 |
| | ACC Thr | ATG Met 210 | GTA Val | TTT Phe | GAA Glu | TGT Cys | ATT Ile 215 | GCT Ala | GGA Gly | TAT Tyr | AGG Arg | CCT Pro 220 | TTT Phe | TTG Leu | CAT His | CAT His | 672 |
| 50 | CTG Leu 225 | CAG Gln | CCA Pro | TTT Phe | Thr | TGG Trp 230 | CAT His | GAG Glu | AAG Lys | ATT Ile | AAG Lys 235 | AAG Lys | AAG Lys | GAT Asp | CCA Pro | AAG Lys 240 | 720 |
| 55 | TGT Cys | ATA Ile | TTT Phe | Ala | TGT Cys 245 | GAA Glu | GAG Glu | ATG Met | Ser | GGA Gly 250 | GAA Glu | GTT Val | CGG Arg | Phe | AGT Ser 255 | AGC Ser | 768 |

| | | | | | CCA | | | | | | | | | | | | 816 |
|----|-----|-----|------------|------------|-------------------|-----|-----|------------|------------|------------|-----|-----|------------|------------|------------|-----|------|
| 5 | His | Leu | Pro | Gln 260 | Pro | Asn | Ser | Leu | Cys 265 | Ser | Leu | Ile | Val | Glu 270 | Pro | Met | |
| J | GAA | AAC | TGG | CTA | CAG | TTG | ATG | TTG | AAT | TGG | GAC | ССТ | CAG | CAG | AGA | GGA | 864 |
| | Glu | Asn | Trp 275 | Leu | Gln | Leu | Met | Leu 280 | Asn | Trp | Asp | Pro | Gln 285 | Gln | Arg | Gly | |
| 10 | | | | | CTT Leu | | | | | | | | | | | | 912 |
| 15 | | | | | AAT Asn | | | | | | | | | | | | 960 |
| | GCA | AAG | АТА | ATT | TCT | TTT | CTG | TTA | CCA | CCT | GAT | GAA | AGT | CTT | CAT | TCA | 1008 |
| 20 | Ala | Lys | Ile | Ile | Ser 325 | Phe | Leu | Leu | Pro | Pro 330 | Asp | Glu | Ser | Leu | His 335 | Ser | |
| | | | | | ATT Ile | | | | | | | | | | | | 1056 |
| 25 | GAA | СТТ | СТТ | TCA | GAG | ACA | GGA | АТТ | тст | СТС | САТ | ССТ | CGG | ΑΑΑ | CCA | GCC | 1104 |
| | | | | | Glu | | | | | | _ | | | | | | |
| 30 | | _ | | | CTA Leu | | | | | | | | | | | | 1152 |
| 35 | | | | | AAA Lys | | | | | | | | | | | | 1200 |
| 40 | | | | | GAT Asp 405 | | | | | | | | | | | | 1248 |
| | | | | | ATA Ile | | | | | | | | | | | | 1296 |
| 45 | | | | | CTA Leu | | | | | | | | | | | | 1344 |
| 50 | | _ | | | TTA Leu | | | | | | | | | | | | 1392 |
| 55 | | | | | TTG Leu | | | | | | | | | | | | 1440 |

| | GAG Glu | TTT Phe | TTT Phe | CAC His | AAA Lys | Ser | ATT | CAG | CTT Leu | GAC Asp | Leu | GAG Glu | AGA Arg | TAC Tyr | AGC Ser 495 | GAG Glu | 1488 |
|----|------------|-------------------|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|------------|------|
| 5 | CAG Gln | ATG Met | ACG Thr | TAT Tyr 500 | Gly | ATA Ile | TCT Ser | TCA Ser | GAA Glu 505 | AAA Lys | ATG Met | CTA Leu | AAA Lys | GCA Ala 510 | TGG Trp | AAA Lys | 1536 |
| 10 | GAA Glu | ATG Met | GAA Glu 515 | Glu | AAG Lys | GCC Ala | ATC Ile | CAC His 520 | Tyr | GCT Ala | GAG Glu | GTT Val | GGT Gly 525 | GTC Val | ATT Ile | GGA Gly | 1584 |
| 15 | TAC Tyr | CTG Leu 530 | GAG Glu | GAT Asp | CAG Gln | ATT Ile | ATG Met 535 | TCT Ser | TTG Leu | CAT His | GCT Ala | GAA Glu 540 | ATC Ile | ATG Met | GGG | CTA Leu | 1632 |
| 20 | G1n 545 | AAG Lys | Ser | Pro | Tyr | Gly 550 | Arg | Arg | Gln | Gly | Asp 555 | Leu | Met | Glu | Ser | Leu 560 | 1680 |
| 25 | Glu | CAG Gln | Arg | Ala | Ile 565 | Asp | Leu | Tyr | Lys | Gln 570 | Leu | Lys | His | Arg | Pro 575 | Ser | 1728 |
| | Asp | CAC His | Ser | Tyr 580 | Ser | Asp | Ser | Thr | Glu 585 | Met | Val | Lys | Ile | Ile 590 | Val | His | 1776 |
| 30 | ACT Thr | GTG Val | CAG Gln 595 | AGT Ser | CAG Gln | GAC Asp | CGT Arg | GTG Val 600 | CTC Leu | AAG Lys | GAG Glu | CTG Leu | TTT Phe 605 | GGT Gly | CAT His | TTG Leu | 1824 |
| 35 | Ser | AAG Lys 610 | Leu | Leu | Gly | Cys | Lys 615 | Gln | Lys | Ile | Ile | Asp 620 | Leu | Leu | Pro | Lys | 1872 |
| 40 | Va1 625 | GAA Glu | Val | Ala | Leu | Ser 630 | Asn | Ile | Lys | Glu | Ala 635 | Asp | Asn | Thr | Val | Met 640 | 1920 |
| 45 | TTC Phe | ATG Met | CAG Gln | GGA Gly | AAA Lys 645 | AGG Arg | CAG Gln | AAA Lys | GAA Glu | ATA Ile 650 | TGG Trp | CAT His | CTC Leu | CTT Leu | AAA Lys 655 | ATT Ile | 1968 |
| | GCC Ala | TGT Cys | ACA Thr | CAG Gln 660 | AGT Ser | TCT Ser | GCC Ala | CGC Arg | TCT Ser 665 | CTT Leu | GTA Val | GGA Gly | TCC Ser | AGT Ser 670 | CTA Leu | GAA Glu | 2016 |
| 50 | GGT Gly | GCA Ala | GTA Val 675 | ACC Thr | CCT Pro | CAG Gln | Thr | TCA Ser 680 | GCA Ala | TGG Trp | CTG Leu | CCC Pro | CCG Pro 685 | ACT Thr | TCA Ser | GCA Ala | 2064 |
| 55 | GAA Glu | CAT His 690 | GAT Asp | CAT His | TCT Ser | Leu | TCA Ser 695 | TGT Cys | GTG Val | GTA Val | ACT Thr | CCT Pro 700 | CAA Gln | GAT Asp | GGG Gly | GAG Glu | 2112 |

| | | | | | ATG | | | | | | | | | | | | 2160 |
|----|------------|-----|-----|------------|------------|------------|----------------|-----|------------|-----|------------|------------|-------|------------|------|------------|------|
| - | Thr 705 | Ser | Ala | Gln | Met | Ile 710 | Glu | Glu | Asn | Leu | Asn 715 | Cys | Leu | Gly | His | Leu 720 | |
| 5 | AGC | ΔСТ | ΔΤΤ | ልጥጥ | CAT | GAG | GCA | דממ | GAG | GAA | CAG | GGC | ידממ | дст | ልጥር | ATG | 2208 |
| | | | | | His | | | | | | | | | | | | 2200 |
| | | | | | 725 | | | | | 730 | | 7 | | | 735 | | |
| 10 | AAT | CTT | GAT | TGG | AGT | TGG | TTA | ACA | GAA | TGG | GTA | CCG | CGG | GCC | CGG | GAT | 2256 |
| | Asn | Leu | Asp | Trp 740 | Ser | Trp | Leu | Thr | Glu 745 | Trp | Val | Pro | Arg | Ala 750 | Arg | Asp | |
| | CCA | CCG | GTC | GCC | ACC | ATG | GTG | AGC | AAG | GGC | GAG | GAG | CTG | TTC | ACC | GGG | 2304 |
| 15 | Pro | Pro | Val | Ala | Thr | Met | Val | Ser | Lys | Gly | Glu | Glu | Leu | Phe | Thr | Gly | |
| | | | 755 | | | | | 760 | | | | | 765 | | | | |
| | | | | | CTG | | | | | | | | | | | | 2352 |
| 20 | Val | | Pro | Ile | Leu | Val | | Leu | Asp | Gly | Asp | | Asn | Gly | His | Lys | |
| 20 | | 770 | | | | | 775 | | | | | 780 | | | | | |
| | | | | | GGC | | | | | | | | | | | | 2400 |
| | 785 | ser | vaı | ser | Gly | 790 | GIY | Glu | GIA | Asp | A1a 795 | Thr | Tyr | GIY | гÀа | ьеи 800 | |
| 25 | 765 | | | | | 790 | | | | | 193 | | | | | 800 | |
| | ACC | CTG | AAG | TTC | ATC | TGC | ACC | ACC | GGC | AAG | CTG | CCC | GTG | CCC | TGG | CCC | 2448 |
| | Thr | Leu | Lys | Phe | Ile | Cys | Thr | Thr | Gly | Lys | Leu | Pro | Val | Pro | Trp | Pro | |
| | | | | | 805 | | | | | 810 | | | | | 815 | | |
| 30 | ACC | CTC | GTG | ACC | ACC | CTG | ACC | TAC | GGC | GTG | CAG | TGC | TTC | AGC | CGC | TAC | 2496 |
| | Thr | Leu | Val | Thr | Thr | Leu | Thr | Tyr | Gly | Val | Gln | Cys | Phe | Ser | Arg | Tyr | |
| | | | | 820 | | | | | 825 | | | | | 830 | | | |
| | | | | | AAG | | | | | | | | | | | | 2544 |
| 35 | Pro | Asp | | Met | Lys | Gln | His | _ | Phe | Phe | Lys | Ser | | Met | Pro | Glu | |
| | | | 835 | | | | | 840 | | | | | 845 | | | | |
| | _ | | _ | _ | GAG | | | | | | | | | _ | | | 2592 |
| 40 | GIY | 850 | vaı | GIN | Glu | Arg | 855 | тте | Pne | Pne | гуѕ | Asp 860 | Asp | GIY | Asn | Tyr | |
| 70 | | 650 | | | | | 033 | | | | | 860 | | | | | |
| | AAG | ACC | CGC | GCC | GAG | GTG | AAG | TTC | GAG | GGC | GAC | ACC | CTG | GTG | AAC | CGC | 2640 |
| | Lys | Thr | Arg | Ala | Glu | Val | Lys | Phe | Glu | Gly | Asp | Thr | Leu | Val | Asn | Arg | |
| Ω | 865 | | | | | 870 | | | | | 875 | | | | | 880 | |
| 45 | . | 0.0 | ama | | | 7 mg | a. a | | | ~~~ | ~~~ | ~~~ | | | omo | 000 | 2600 |
| | | | | | GGC Gly | | | | | | | | | | | | 2688 |
| | 116 | Giu | пец | цуѕ | 885 | 116 | Asp | Pne | цуѕ | 890 | Asp | GIA | ASII | 116 | 895 | GIY | |
| | | | | | | | | | | | | | | | 0,0 | | |
| 50 | CAC | AAG | CTG | GAG | TAC | AAC | TAC | AAC | AGC | CAC | AAC | GTC | TAT | ATC | ATG | GCC | 2736 |
| | His | Lys | Leu | Glu | Tyr | Asn | \mathtt{Tyr} | Asn | Ser | His | Asn | Val | Tyr | Ile | Met | Ala | |
| | | | | 900 | | | | | 905 | | | | | 910 | | | |
| | GNG | מממ | CAC | 777 | AAC | acc | אידים | 770 | ome | 777 | mma | מ מ מ | איייט | 000 | C2 C | ስ አ C | 2701 |
| 55 | | | | | Asn | _ | | | | | | | | | | | 2784 |
| | | | 915 | _1 = | | 2 | | 920 | | | | _10 | 925 | 9 | | | |

238

| 5 | A7 | C GA le Gl 93 | u As | AC GG sp Gl | C AG y Se | C GT r Va | G CA 1 G1 93 | n Le | C GC u Al | C GA | C CA | С ТА s Ту 94 | r Gl | G CA | G AA n As | C ACC | 2832 |
|----|----------------|---------------------|---------------------|----------------|------------------------|---------------------|--------------------|---------------------|---------------------|--------------|--------------|--------------------|-------|-------------------------------|--------------|-----------------------|------|
| 3 | CC Pr 94 | 0 11 | C GG e Gl | C GA y As | C GG p Gl | C CC y Pro 95 | o va | G CT l Le | G CT u Le | G CC u Pr | C GA O As | p As | C CA | C TA | C CI r Le | G AGC u Ser 960 | 2880 |
| 10 | 111 | ı Gı | 11 56 | I AI | а леі 96! | u Sei | с Бу | s As | p Pr | o As 97 | n Gli 0 | и ГУ | s Arg | g Ası | 97 | - | |
| 15 | va | T De | u be | 98 | u Pne | e val | ACC Th | C GC | G GC a Ala 98 | a Gl | G ATO | C AC | r CT(| GG(Gl ₃ 990 | / Me | G GAC t Asp | 2976 |
| 20 | | G CTO | | r Ly: | G TAA | A | | | | | | | | | | | 2991 |
| 25 | | | (i) S (A) (B) | SEQUE LEN | NFORM ENCE NGTH: | CHAR 996 mino | ACTE ami aci | RIST .no a .d | ICS: | | :123: | | | | | | |
| 30 | | (| (D) | TOP | CULE | Y: l TYP | inea E: p | rote | in | | | | | | | | |
| 35 | Met | | | | ENCE | | | | | | | | Gly | Pro | Trp | Glu | |
| 40 | Met | Arg | Glu | Arg 20 | Leu | Gly | Thr | Gly | Gly 25 | 10 Phe | Gly | Asn | Val | Cys | 15 Leu | Tyr | |
| 40 | | | 33 | | Leu Lys | | | 40 | | | | | 45 | | | | |
| 45 | Met 65 | Lys | Lys | Leu | Asn | His 70 | Ala | Asn | Val | Val | Lys | 60 Ala | Cys | Asp | Val | Pro | |
| | | | | Gly | Ile 85 Gly | | | | | 90 | | | | | 0.5 | | |
| 50 | Сув | Cys | Gly 115 | Leu | Lys | Glu | Ser | Gln 120 | 105 Ile | Leu | Ser | Leu | Leu | 110 Ser | Asp | Ile | |
| | | 130 | | | Arg Asn | | 135 | | | | | 140 | Ile | | | | |
| 55 | 443 | | | | Asp | T20 | | | | | 155 | | | | | 1.00 | |

| | | | | | 165 | | | | | 170 | | | | | 175 | |
|----|------------|----------|----------|------------|---------|--------------|------|------|-------|-----------|------------|--------------|-------------|------------|-------------|-------|
| | Lou | Cva | Thr | Ser | 165 | Wa l | Gly | Thr | T 011 | 170 | There | LOW | ח ז ח | Dro | 175 | Len |
| | Leu | Cys | 1111 | 180 | FIIC | Val | Gry | 1111 | 185 | GIII | TAT | Leu | міа | 190 | GIU | пеа |
| | Phe | Glu | Asn | Lys | Pro | Tvr | Thr | Ala | | Val | Asp | Tvr | Trp | | Phe | Glv |
| 5 | | | 195 | -7- | | -1- | | 200 | | | | -1- | 205 | | | |
| | Thr | Met | Val | Phe | Glu | Cys | Ile | Ala | Gly | Tyr | Arg | Pro | Phe | Leu | His | His |
| | | 210 | | | | | 215 | | | | _ | 220 | | | | |
| | Leu | Gln | Pro | Phe | Thr | Trp | His | Glu | Lys | Ile | Lys | Lys | Lys | Asp | ${\tt Pro}$ | Lys |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| 10 | Cys | Ile | Phe | Ala | _ | Glu | Glu | Met | Ser | - | Glu | Val | Arg | Phe | | Ser |
| | *** | . | D | 01 | 245 | 3 | O | | G | 250 | • | T 3 . | **- 7 | a 1 | 255 | 14-5 |
| | HIS | ьeu | Pro | Gln 260 | PIO | ASII | ser | Leu | 265 | ser | Leu | 116 | vaı | 270 | PIO | Met |
| | Glu | Asn | Trn | Leu | Gln | Leu | Met | Leu | | Trp | Asn | Pro | Gln | | Ara | Glv |
| 15 | | 11011 | 275 | | | | | 280 | | | | | 285 | | | , |
| | Gly | Pro | Val | Asp | Leu | Thr | Leu | Lys | Gln | Pro | Arg | Cys | Phe | Val | Leu | Met |
| | | 290 | | | | | 295 | | | | | 300 | | | | |
| | Asp | His | Ile | Leu | Asn | Leu | Lys | Ile | Val | His | Ile | Leu | Asn | Met | Thr | Ser |
| | 305 | | _ | _ | | 310 | | | | | 315 | | | | | 320 |
| 20 | Ala | Lys | Ile | Ile | | Phe | Leu | Leu | Pro | | Asp | Glu | Ser | Leu | | Ser |
| | T 011 | ~1 m | Cox | 7 ~~~ | 325 | C1 | 7 ~~ | C1 | mh.~ | 330 | 710 | 7.00 | The se | C111 | 335 | Gln |
| | геп | GIII | 261 | Arg | 116 | GIU | Arg | GIU | 345 | СТУ | 116 | ASII | 1111 | 350 | 261 | GIII |
| | Glu | Leu | Leu | Ser | Glu | Thr | Glv | Ile | | Leu | Asp | Pro | Ara | | Pro | Ala |
| 25 | | | 355 | | | | 2 | 360 | | | | | 365 | • | | |
| | Ser | Gln | Cys | Val | Leu | Asp | Gly | Val | Arg | Gly | Суз | Asp | Ser | Tyr | Met | Val |
| | | 370 | | | | | 375 | | | | | 380 | | | | |
| | | Leu | Phe | Asp | Lys | | Lys | Thr | Val | Tyr | | Gly | Pro | Phe | Ala | |
| 20 | 385 | 0 | . | 0 | 7 | 390 | 17-1 | n | m | T3 - | 395 | ~1 - | > | | T | 400 |
| 30 | Arg | ser | Leu | Ser | 405 | Cys | vai | Asn | туг | 410 | vai | GIN | Asp | ser | цу S | TIE |
| | Gln | Leu | Pro | Ile | | Gln | Leu | Ara | Lvs | | Trp | Ala | Glu | Ala | | His |
| | | | | 420 | | | | | 425 | | | | | 430 | | |
| | Tyr | Val | Ser | Gly | Leu | Lys | Glu | Asp | Tyr | Ser | Arg | Leu | Phe | Gln | Gly | Gln |
| 35 | | | 435 | | | | | 440 | | | | | 445 | | | |
| | Arg | | Ala | Met | Leu | Ser | | Leu | Arg | Tyr | Asn | | Asn | Leu | Thr | Lys |
| | | 450 | • | m\ | T | 7 3 - | 455 | 71- | 0 | 01 | a 1 | 460 | * | 77- | | T 011 |
| | мес 465 | гÀг | Asn | Thr | ren | 470 | ser | Ala | ser | GIN | 475 | Leu | Lys | Ата | гуя | 480 |
| 40 | | Phe | Phe | His | Lvs | | Tle | Gln | Leu | Asp | | Glu | Ara | Tvr | Ser | |
| | 014 | | | | 485 | | | | | 490 | | | •• | -1- | 495 | |
| | Gln | Met | Thr | Tyr | Gly | Ile | Ser | Ser | Glu | Lys | Met | Leu | Lys | Ala | Trp | Lys |
| | | | | 500 | | | | | 505 | | | | | 510 | | |
| | Glu | Met | Glu | Glu | Lys | Ala | Ile | His | Tyr | Ala | Glu | Val | Gly | Val | Ile | Gly |
| 45 | | | 515 | | _ | | | 520 | | | | | 525 | | | _ |
| | Tyr | | Glu | Asp | GIn | He | | Ser | Leu | His | Ala | | Ile | Met | GIY | Leu |
| | Gla | 530 | Sar | Pro | Тиг | Gly | 535 | 7~4 | Gl n | alv | λαν | 540 | Mot | Glu | Ser | Len |
| | 545 | nys | 361 | FIU | 1 Y L | 550 | Arg | Arg | GIII | сту | 555 | пеа | Mec | GIU | JCI | 560 |
| 50 | | Gln | Arq | Ala | Ile | | Leu | Tyr | Lys | Gln | | Lys | His | Arq | Pro | |
| | | | _ | | 565 | - | | - | - | 570 | | - | | _ | 575 | |
| | Asp | His | Ser | Tyr | Ser | Asp | Ser | Thr | Glu | Met | Val | Lys | Ile | Ile | Val | His |
| | | | | 580 | | _ | | = | 585 | | | | | 590 | | _ |
| CE | Thr | Val | | Ser | Gln | Asp | Arg | | Leu | Lys | Glu | Leu | | Gly | His | Leu |
| 55 | ee | T | 595 | Less | Glar. | C | T | 600 | T | T1. | т1. | 7 c= | 605 | Torr | D~~ | Lve |
| | ser | пÀв | Leu | Leu | GTÅ | Cys | пàв | GIII | гÀв | тте | 116 | Asp | ոեն | neu | PLO | nys |

```
615
                                                620
      Val Glu Val Ala Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met
                       630
                                 635
      Phe Met Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile
 5
                     645
                                       650
      Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu
                 660
                                   665
      Gly Ala Val Thr Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala
                                680
                                                   685
10
      Glu His Asp His Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu
                      695
      Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu
                        710
                                          715
      Ser Thr Ile Ile His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met
15
                   725
                                       730
      Asn Leu Asp Trp Ser Trp Leu Thr Glu Trp Val Pro Arg Ala Arg Asp
                         745
      Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
                                760
20
      Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
                            775
      Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
                        790
                                           795
      Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
25
                    805
                                       810
     Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
                820
                                    825
                                                830
      Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
                               840
30
     Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
                           855
                                              860
     Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
                        870
                                          875
     Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
35
                    885
                                       890
     His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
                                   905
     Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
                               920
                                     925
40
     Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
                           935
                                               940
     Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
                        950
                                          955
     Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
45
                    965
                                       970
     Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
              980
                                    985
     Glu Leu Tyr Lys
             995
50
```

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1908 base pairs
- 55 (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

241

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

35

55

(A) NAME/KEY: Coding Sequence(B) LOCATION: 1...1905

(D) OTHER INFORMATION:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

20 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC
Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
35 40 45

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC CC CS Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG
Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
30 65 70 75 80

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG
Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
85
90
95

CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu

100 105 110

40 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384
Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 125

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 - 45 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 160

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
165 170 175

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC 576

| | | | | | | | | | | 242 | | | | | | | |
|----|-----------------------|--------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------------|-------------------|---------------------|--------------|--------------------|---------------------|-----------------------|--------------|--------------------|-----------------------|-------------|
| | Va | 1 G | ln Le | eu A] 18 | la As 30 | p Hi | в Ту | r Gl | n Gl 18 | n As | n Th | ır P | ro II | le G1 | | sp Gly | |
| 5 | | | 19 | 5 | u Pi | O AS | p As | n H1 20 | .s Ту 0 | r Le | u Se | r Tì | r G] 20 | ln Se | r Al | CC CTG .a Leu | 624 |
| 10 | AG Se: | C AA r Ly 21 | o Ao | .C CC p Pr | C AA O As | C GA | G AA u Ly 21 | s Ar | C GA g As | T CA p Hi | C AT s Me | G GT t Va 22 | 1 Le | G CI u Le | G GA u Gl | G TTC u Phe | 672 |
| 15 | GT(Va. 225 | | C GC r Al | C GC a Al | C GG a Gl | G ATO y Ile 230 | = In | r CT | C GG u Gl | C AT | G GA t As 23 | p Gl | G CT u Le | G TA u Ty | C AA r Ly | G TCC s Ser 240 | 720 |
| | GG# Gly | A CT | C AG | A TC | r CGA r Arg 245 | A ATS | CAZ Glr | A GC | T TC | C ATO | t Se | C GA r Gl | G AC u Th | G GT r Va | C AT 1 I1 25 | C ATG e Met 5 | 768 |
| 20 | AGC Ser | GA(| 3 ACC | G GT(C Val 260 | r TT6 | TGT Cys | TCC Ser | AGC Ser | C CGC Arg 265 | y Ala | C AC | r GT | G ATO | G CT | ту: | r GAT | 816 |
| 25 | GAT Asp | Gl) | 2 AAC / Asr 275 | LLys | G CGA | TGG Trp | CTC | CCT Pro |) Ala | GGC Gly | C ACC | G GG | r ccc y Pro 285 | Glr | GC0 Ala | TTC Phe | 864 |
| 30 | AGC Ser | CGC Arg 290 | | CAC Gln | ATC Ile | TAC Tyr | CAC His 295 | AAC Asn | CCC Pro | ACG Thr | GCC Ala | CAA S Asr 300 | ı Ser | TTT | CGC Arg | GTC Val | 912 |
| 35 | 305 | 1 | 9 | Буз | Mer | 310 | PIO | Asp | Gin | Gln | Val 315 | Val | . Ile | Asn | Cys | GCC Ala 320 | 960 |
| | | , 41 | nig | GIY | 325 | ьуѕ | Tyr | Asn | Gln | Ala 330 | Thr | Pro | Asn | Phe | His 335 | CAG Gln | 1008 |
| 40 | • | 5 | | 340 | CGC Arg | GIII | vai | irp | 345 | Leu | Asn | Phe | Gly | Ser 350 | Lys | Glu | 1056 |
| 45 | GAT Asp | GCG Ala | GCC Ala 355 | CAG Gln | TTT Phe | GCC Ala | GCC Ala | GGC Gly 360 | ATG Met | GCC Ala | AGT Ser | GCC Ala | CTA Leu 365 | GAG Glu | GCG Ala | TTG Leu | 1104 |
| 50 | GAA Glu | GGA Gly 370 | GGT Gly | GGG Gly | CCC Pro | PIO | CCA Pro 375 | CCC Pro | CCA Pro | GCA Ala | CTT Leu | CCC Pro 380 | ACC Thr | TGG Trp | TCG Ser | GTC Val | 1152 |
| 55 | CCG . Pro . 385 | AAC Asn | GGC Gly | CCC Pro | DCI | CCG Pro | GAG Glu | GAG Glu | GTG Val | GAG Glu | CAG Gln 395 | CAG Gln | AAA Lys | AGG Arg | CAG Gln | CAG Gln 400 | 1200 |
| | CCC (| GGC | CCG | TCG | GAG · | CAC A | АТА | GAG | CGC | CGG | GTC | TCC | AAT | GCA | GGA | GGC | 1248 242 |

| | | | | | | | | | | | L-10 | | | | | | | |
|-----|----|----|-----|------------|------------|------------|------------|-----|------------|------------|------------|-----|-----|------------|------------|------------|-----|------------|
| | P | co | Gly | Pro | Ser | Glu 405 | His | Ile | Glu | Arg | Arg 410 | Val | Ser | Asn | Ala | Gly 415 | Gly | |
| ; | _ | | | | Pro | | GCT Ala | | | Pro | | | | | Gly | | | 1296 |
| | | | | | | | CCC | | | | | | | | | _ | _ | 1344 |
| 10 | | co | Pro | Pro 435 | Gly | Pro | Pro | Pro | Pro 440 | Pro | Gly | Leu | Pro | Pro 445 | Ser | Gly | Val | |
| | | | | | | | GGA Gly | | | | | | | | | | | 1392 |
| 1 | C' | | | | | | GGC Gly | | | | | | | | | | | 1440 |
| 0.4 | 4 | 55 | | | | | 470 | | _ | _ | - | 475 | | _ | | | 480 | |
| 20 | | | | | | | GCT Ala | | | | | | | | | | | 1488 |
| 2 | | | | | | | GGG Gly | | | | | | | | | | | 1536 |
| | A | 3C | GGA | GGT | 500 GGG | GGA | CTC | ATG | GAA | 505 GAG | ATG | AAC | GCC | ATG | 510 CTG | GCC | CGG | 1584 |
| 30 | | er | Gly | Gly 515 | Gly | Gly | Leu | Met | Glu 520 | Glu | Met | Asn | Ala | Met 525 | Leu | Ala | Arg | |
| | | | | Lys | | | CAA Gln | | | | | | | | | _ | | 1632 |
| 3 | G | | AAT | CAG | | | CCA | GAG | | | | | GCC | | | _ | | 1680 |
| | 5 | 45 | | | | | Pro 550 | | | | | 555 | | | | | 560 | |
| 40 | | | | | | | GAG Glu | | | | | | | | | | | 1728 |
| 4 | | | | | | | ACC Thr | | | | | | | | Thr | | | 1776 |
| | T | CC | AGT | GAT | 580 TAC | TCG | GAC | CTA | CAG | 585 AGG | GTG | AAA | CAG | GAG | 590 CTT | CTG | GAA | 1824 |
| 5 | | er | Ser | Asp 595 | Tyr | Ser | Asp | Leu | Gln 600 | Arg | Val | Lys | Gln | Glu 605 | Leu | Leu | Glu | |
| | | | | | | | TTG Leu | | | | | | | | | | - | 1872 |
| 5 | | гC | | CAG | GAG | CTG | AGG | | CGG | GGT | TCT | ccc | | | | | | 1908 24 |
| | | | | | | | | | | | | | | | | | | 24 |

244

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

5 (2) INFORMATION FOR SEQ ID NO:125:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 635 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

| | Ţ | | Ser | | 5 | | | | | 10 | | | | | 15 | |
|----|-----|-----|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 20 | | | Leu | 20 | | | | | 25 | | | | | 3.0 | Ser | |
| | | | Glu 35 | | | | | 40 | | | | | 45 | | | |
| 25 | | 50 | Thr | | | | 55 | | | | | 60 | | | | |
| | 03 | | Tyr | | | 70 | | | | | 75 | | | | | B O |
| | | | Asp | | 85 | | | | | 90 | | | | | 95 | Glu |
| 30 | | | Ile | 100 | | | | | 105 | | | | | 110 | | |
| | | | Phe 115 | | | | | 120 | | | | | 125 | | | |
| 35 | | 130 | Phe | | | | 135 | | | | | 140 | | | | |
| | 145 | | Asn | | | 150 | | | | | 155 | | | | | 160 |
| | | | Lys | | 165 | | | | | 170 | | | | | 175 | Ser |
| 40 | | | Leu | 180 | | | | | 185 | | | | | 190 | Asp | |
| | | | Leu 195 | | | | | 200 | | | | | 205 | Ser | | |
| 45 | | 210 | Asp | | | | 215 | | | | | 220 | Leu | | | |
| | 225 | | Ala | | | 230 | | | | | 235 | Glu | | | | 240 |
| | | | Arg | | 245 | | | | | 250 | Ser | | | | 255 | Met |
| 50 | | | Thr | 260 | | | | | 265 | | | | | 270 | Tyr | |
| | | | Asn 275 | | | | | 280 | Ala | | | | 285 | Gln | | |
| 55 | | 290 | Val | | | | 295 | | | | | 300 | Ser | | | |
| | Val | Gly | Arg | Lys | Met | Gln | Pro | Asp | Gln | Gln | Val | Val | Ile | Asn | Cys | Ala |

245

```
310
                                       315
     Ile Val Arg Gly Val Lys Tyr Asn Gln Ala Thr Pro Asn Phe His Gln
                 325
                                  330
     Trp Arg Asp Ala Arg Gln Val Trp Gly Leu Asn Phe Gly Ser Lys Glu
5
                               345
     Asp Ala Ala Gln Phe Ala Ala Gly Met Ala Ser Ala Leu Glu Ala Leu
           355
                   360
                                    365
     Glu Gly Gly Pro Pro Pro Pro Ala Leu Pro Thr Trp Ser Val
                        375
                                          380
10
     Pro Asn Gly Pro Ser Pro Glu Glu Val Glu Gln Gln Lys Arg Gln Gln
                     390
                                       395
     Pro Gly Pro Ser Glu His Ile Glu Arg Arg Val Ser Asn Ala Gly Gly
                  405
                         410
     Pro Pro Ala Pro Pro Ala Gly Gly Pro Pro Pro Pro Pro Gly Pro Pro
15
            420
                               425
     Pro Pro Pro Gly Pro Pro Pro Pro Gly Leu Pro Pro Ser Gly Val
                                    445
                  440
     Pro Ala Ala His Gly Ala Gly Gly Pro Pro Pro Ala Pro Pro
20
     Leu Pro Ala Ala Gln Gly Pro Gly Gly Gly Ala Gly Ala Pro Gly
                    470
                                       475
     Leu Ala Ala Ile Ala Gly Ala Lys Leu Arg Lys Val Ser Lys Gln
                                   490
     Glu Glu Ala Ser Gly Gly Pro Thr Ala Pro Lys Ala Glu Ser Gly Arg
25
              500
                               505
                                                 510
     Ser Gly Gly Gly Leu Met Glu Glu Met Asn Ala Met Leu Ala Arg
                                              525
                             520
     Arg Arg Lys Ala Thr Gln Val Gly Glu Lys Thr Pro Lys Asp Glu Ser
                         535
                                           540
30
     Ala Asn Gln Glu Pro Glu Ala Arg Val Pro Ala Gln Ser Glu Ser
             550
                                     555
     Val Arg Arg Pro Trp Glu Lys Asn Ser Thr Thr Leu Pro Arg Met Lys
                                   570
                  565
     Ser Ser Ser Ser Val Thr Thr Ser Glu Thr Gln Pro Cys Thr Pro Ser
35
        580 585 590
     Ser Ser Asp Tyr Ser Asp Leu Gln Arg Val Lys Gln Glu Leu Leu Glu
                             600
     Glu Val Lys Lys Glu Leu Gln Lys Val Lys Glu Glu Ile Ile Glu Ala
               615
40
     Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro
             (2) INFORMATION FOR SEQ ID NO:126:
```

45 (i) SEQUENCE CHARACTERISTICS:

50

55

- (A) LENGTH: 1329 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:
 - (A) NAME/KEY: Coding Sequence(B) LOCATION: 1...1326
 - (D) OTHER INFORMATION:

246

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

| | | | | _ | | | | | ٠٠. 5 | ro Ti | J NO | :126 | : | | | | |
|----|-------------------|-------------------|-------------------|----------------------|---------------------|-------------------|-------------------|-------------------|------------------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|--------------------|
| 5 | ATO Met | GT(| G AGO | C AAC | G GGG G Gly 5 | C GAO | G GAC | G CTO | TTC Phe | C ACC Thi | C GGG | G GT(| G GT | G CCO | C ATO | C CTG e Leu | 48 |
| 10 | GTC Val | GAC Glu | G CTO | G GAC 1 Asp 20 | GGC Gly | C GA(| C GTA | A AAC . Asr | GGG Gl ₃ 25 | C CAC | AAC Lys | TTC Phe | C AGO | C GTO Val | TC(| C GGC r Gly | 96 |
| 15 | GAG Glu | GGC Gly | GAC Glu 35 | GGC Gly | GAT Asp | GCC Ala | ACC Thr | TAC Tyr 40 | GGC Gly | AAC Lys | CTC Leu | ACO Thr | C CTC Leu 45 | AAC Lys | TTO Phe | C ATC | 144 |
| | TGC Cys | ACC Thr 50 | ACC Thr | GGC Gly | AAG Lys | CTG Leu | Pro | GTG Val | Pro | TGG Trp | CCC Pro | ACC Thr | CTC | GTG Val | ACC Thr | ACC Thr | 192 |
| 20 | CTG Leu 65 | ACC | TAC Tyr | GGC | GTG Val | CAG Gln 70 | TGC Cys | TTC Phe | AGC Ser | CGC Arg | TAC Tyr 75 | CCC Pro | GAC Asp | CAC | ATG Met | AAG Lys 80 | 240 |
| 25 | CAG Gln | CAC His | GAC Asp | TTC Phe | TTC Phe 85 | AAG Lys | TCC Ser | GCC Ala | ATG Met | CCC Pro 90 | GAA Glu | GGC Gly | TAC Tyr | GTC Val | CAG Gln 95 | GAG Glu | 288 |
| 30 | CGC Arg | ACC Thr | ATC Ile | TTC Phe 100 | TTC Phe | AAG Lys | GAC Asp | GAC Asp | GGC Gly 105 | AAC Asn | TAC Tyr | AAG Lys | ACC Thr | CGC Arg 110 | GCC Ala | GAG Glu | 336 |
| 35 | GTG Val | AAG Lys | TTC Phe 115 | GAG Glu | GGC Gly | GAC Asp | ACC Thr | CTG Leu 120 | GTG Val | AAC Asn | CGC Arg | ATC Ile | GAG Glu 125 | CTG Leu | AAG Lys | GGC Gly | 384 |
| | 110 | GAC Asp 130 | TTC Phe | AAG Lys | GAG Glu | GAC Asp | GGC Gly 135 | AAC Asn | ATC Ile | CTG Leu | GGG Gly | CAC His 140 | AAG Lys | CTG Leu | GAG Glu | TAC Tyr | 432 |
| 40 | AAC Asn 145 | TAC Tyr | AAC Asn | AGC Ser | CAC His | AAC Asn 150 | GTC Val | TAT Tyr | ATC Ile | ATG Met | GCC Ala 155 | GAC Asp | AAG Lys | CAG Gln | AAG Lys | AAC Asn 160 | 480 |
| 45 | GGC . | ATC Ile | AAG Lys | vaı | AAC Asn 165 | TTC Phe | AAG Lys | ATC Ile | CGC Arg | CAC His 170 | AAC Asn | ATC Ile | GAG Glu | GAC Asp | GGC Gly 175 | AGC Ser | 528 |
| 50 | GTG (| CAG Gln | CTC Leu | GCC Ala 180 | GAC Asp | CAC His | TAC Tyr | Gln | CAG Gln 185 | AAC Asn | ACC Thr | CCC Pro | ATC Ile | GGC Gly 190 | GAC Asp | GGC Gly | 576 |
| 55 | CCC (| VAI | CTG Leu 195 | CTG Leu | CCC Pro | GAC . Asp . | Asn] | CAC His | TAC Tyr | CTG . Leu | AGC . Ser | Thr | CAG Gln 205 | TCC Ser | GCC Ala | CTG Leu | 624 |
| | AGC A | AAA | GAC | ccc i | AAC (| GAG . | AAG (| CGC (| GAT (| CAC / | ATG (| GTC | CTG | CTG | GAG | TTC | 672 24 6 |

SUBSTITUTE SHEET (RULE 26)

| | Ser | Lys 210 | Asp | Pro | Asn | Glu | Lys 215 | Arg | Asp | His | Met | Val 220 | Leu | Leu | Glu | Phe | |
|----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-------------------|-----|-----|-------------|
| 5 | | | | | | | | | | | | | | TAC Tyr | | | 720 |
| 10 | | | | | | | | | | | | | | CGG Arg | | | 768 |
| 15 | | - | | | | | | | | | | | | TTG Leu 270 | | | 816 |
| 15 | | | | | | | | | | | | | | ACA Thr | | | 864 |
| 20 | | | | | | | | | | | | | | GTA Val | _ | | 912 |
| 25 | | | | | | | | | | | | | | CTG Leu | | | 960 |
| 30 | | | | | | | | | | | | | | TCC Ser | | | 1008 |
| 25 | | | | | | | | | | | | | | CCA Pro 350 | | | 1056 |
| 35 | | | | | | | | | | | | | | AAT Asn | | | 1104 |
| 40 | | - | | | | | | | | | | | | AAG Lys | | | 1152 |
| 45 | | | | | | | | | | | | | | AAC Asn | | _ | 1200 |
| 50 | | | | | | | | | | | | | | GAT Asp | | | 1248 |
| | | | | | | | | | | | | | | GCT Ala 430 | | | 1296 |
| 55 | GGG | AAG | AAA | AAA | TCT | GGT | TGC | CTT | GTC | TTG | TGA | | | | | | 1329 247 |

248

Gly Lys Lys Lys Ser Gly Cys Leu Val Leu 435 440

```
5 (2) INFORMATION FOR SEQ ID NO:127:
```

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 442 amino acids
 - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

| Met | Val | Ser | Lys | Gly | Glu | Glu | Leu | Phe | Thr | Glv | Val | Val | Pro | Ile | τ. |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| 1 | | | | 5 | | | | | 3.0 | -1 | | | | | - |
| | | | | | | | | | 10 | | | | | 15 | |

- 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
 20 25 30
- Glu Gly Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
- Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 50 55
- Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
 - Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
 85 90 95
- 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
 100 105 110
 - Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
 115 120 125
- Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

 135 130 135 140
 - Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 145 150 155 160
 - Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 175
- 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
 180 185 190
 - Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 195 200 205
- Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Glu Phe
 210 215 220
 - Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
 225 230 235 240
- Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys
 245 250 255

 Leu Val Ile Val Gly Non G
- 50 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 260 265 270
- Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu 295 300
 Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

| | | | | | | | | | | 243 | | | | | | | | |
|----|------------|------------|----------------|------------|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|----|---|
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | | |
| | Leu | Ser | Tyr | Pro | Asp 325 | Thr | Asp | Val | Ile | Leu 330 | Met | Cys | Phe | Ser | Ile 335 | Asp | | |
| 5 | Ser | Pro | Asp | Ser 340 | Leu | Glu | Asn | Ile | Pro 345 | | Lys · | Trp | Thr | Pro 350 | Glu | Val | | |
| | Lys | His | Phe 355 | | Pro | Asn | Val | Pro 360 | | Ile | Leu | Val | Gly 365 | Asn | Lys | Lys | | |
| | Asp | Leu 370 | | Asn | Asp | Glu | His 375 | | Arg | Arg | Glu | Leu 380 | | Lys | Met | Lys | | |
| 10 | Gln 385 | | Pro | Val | Lys | Pro 390 | | Glu | Gly | Arg | Asp 395 | Met | Ala | Asn | Arg | Ile 400 | | |
| | | Ala | Phe | Gly | Tyr 405 | | Glu | Cys | Ser | Ala 410 | | Thr | Lys | Asp | Gly 415 | | | |
| 15 | Arg | Glu | Val | Phe 420 | | Met | Ala | Thr | Arg 425 | | Ala | Leu | Gln | Ala 430 | | Arg | | |
| .0 | Gly | Lys | Lys 435 | | Ser | Gly | Сув | Leu 440 | _ | Leu | | | | 150 | | | | |
| 00 | | | (2) | INI | FORM | OITA | 1 FO | R SEC | Q ID | NO: | L28: | | | | | | | |
| 20 | | (: | | - | ICE (| | | | | | | | | | | | | |
| | | | (B) | TYPI | STH: S: nu | icle: | ic a | cid | | | | | | | | | | |
| 25 | | | | | ANDEI | | | _ | 2 | | | | | | | | | |
| | | | ii) N ix) N | | CULE JRE: | TYPI | E: cI | DNA | | | | | | | | | | |
| 30 | | | (B) | LO | ME/KI CATIO HER : | ON: | ı: | 1137 | equei | nce | | | | | | | | |
| | | (2 | ki) S | SEQUI | ENCE | DESC | CRIP | rion | : SEC | Q ID | NO: | 128: | | | | | | |
| 35 | ΔΤС | GAC | רמיד | ጥልጥ | СУТ | ידריד | CAG | CDD | ACC | ממ | CDT | TAC | ልጥር | CAG | CCA | GAD | 4 | 8 |
| | | | | | | | | | | | | Tyr | | | | _ | 1 | • |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | | |
| 40 | | | | | | | | | | | | GCC Ala | | _ | | | 9 | 6 |
| | Gru | Asp | Пр | 20 20 | nrg | ASP | пец | пец | 25 | Asp | FIU | AIG | TTP | 30 | БуЗ | GIII | | |
| | _ | | | | | _ | _ | | | | | CAC | | | | _ | 14 | 4 |
| 45 | Gln | Arg | Lys 35 | Thr | Phe | Thr | Ala | Trp 40 | Cys | Asn | Ser | His | Leu 45 | Arg | Lys | Ala | | |
| | | | | | | | | | | | | CGG | | | | | 19 | 2 |
| 50 | Gly | Thr 50 | Gln | Ile | Glu | Asn | 11e 55 | Glu | Glu | Asp | Phe | Arg 60 | Asp | GIA | Leu | Lys | | |
| | | | | | | | | | | | | CGC | | | | | 24 | 0 |
| | Leu 65 | Met | Leu | Leu | Leu | 70 | vaí | lle | ser | Gly | Glu 75 | Arg | Leu | Ala | ràs | Pro 80 | | |
| 55 | GAG | CGA | GGC | AAG | ATG | AGA | GTG | CAC | AAG | ATC | TCC | AAC | GTC | AAC | AAG | GCC | 28 | 8 |
| | | | | | | | | | | | | | | | | | | 2 |

| | | | | | | | | | | 25 | | | | | | | |
|----|-------------------|-------------------|-------------------|---------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|------------|
| | G1 | u A: | rg G | ly Ly | /s Me 85 | et Ar | g Va | l Hi | s Ly | /s I] 90 | le Se | er As | n Va | l As | n Ly 95 | /s Ala | ı |
| 5 | | | | 10 | 0 | .a 5e | т пу | S GI | y va 10 | 11 Ly 5 | s Le | u Va | l Se | r Il 11 | e G1 0 | SA GCC y Ala | |
| 10 | | | 11 | .5 | ± A3 | p GI | y As | 11 va 12 | 0 т г | s Me | t Th | r Le | u Gly 12! | y Me 5 | t Il | C TGG e Trp | |
| 15 | | 13 | 0 | C 25 | u AI | g AL | 13: | p Pro 5 | o Pro | o Va | l Ala | a Th: | r Met O | : Va | l Se | C AAG r Lys | 432 |
| | 145 | 5 | | . . . | u File | 150 |) | y va. | L Va. | l Pro | 0 Ile 159 | € Let 5 | ı Val | Glı | ı Lei | G GAC u Asp 160 | 480 |
| 20 | -, | 7 | , ,,, | ı noı | 165 | HIS | , rys | s Pne | e Ser | 7 Val 170 | l Ser | Gly | , Glu | Gly | / Glu | | 528 |
| 25 | GAT Asp | GC0 | C ACC | TAC Tyr 180 | . Ory | AAG Lys | CTC Leu | ACC Thr | CTG Leu 185 | ггуз | TTC Phe | : ATC | TGC Cys | ACC Thr 190 | Thr | GGC Gly | 576 |
| 30 | AAG Lys | CTC | CCC Pro | • • • • • | Pro | TGG Trp | CCC Pro | ACC Thr 200 | CTC Leu | GTG Val | ACC Thr | ACC Thr | CTG Leu 205 | ACC Thr | TAC | GGC | 624 |
| 35 | | 210 | | | 561 | Arg | 215 | Pro | Asp | His | Met | Lys 220 | CAG Gln | His | Asp | Phe | 672 |
| | TTC Phe 225 | AAG Lys | TCC Ser | GCC Ala | ATG Met | CCC Pro 230 | GAA Glu | GGC Gly | TAC Tyr | GTC Val | CAG Gln 235 | GAG Glu | CGC Arg | ACC Thr | ATC Ile | TTC Phe 240 | 720 |
| 40 | TTC Phe | AAG Lys | GAC Asp | GAC Asp | GGC Gly 245 | AAC Asn | TAC Tyr | AAG Lys | ACC Thr | CGC Arg 250 | GCC Ala | GAG Glu | GTG Val | AAG Lys | TTC Phe 255 | GAG Glu | 768 |
| 45 | GGC Gly | GAC Asp | ACC Thr | CTG Leu 260 | GTG Val | AAC Asn | CGC Arg | ATC Ile | GAG Glu 265 | CTG Leu | AAG Lys | GGC Gly | ATC Ile | GAC Asp 270 | TTC Phe | AAG Lys | 816 |
| 50 | GAG Glu | GAC Asp | GGC Gly 275 | AAC Asn | ATC Ile | CTG Leu | GGG Gly | CAC His 280 | AAG Lys | CTG Leu | GAG Glu | Tyr | AAC Asn 285 | TAC Tyr | AAC Asn | AGC Ser | 864 |
| 55 | CAC His | AAC Asn 290 | GTC Val | TAT Tyr | ATC . | net. | GCC Ala 295 | GAC Asp | AAG Lys | CAG Gln | Lys . | AAC Asn 300 | GGC 1 Gly : | ATC . | AAG Lys | GTG Val | 912 |
| | AAC : | FTC | AAG | ATC | CGC (| CAC 2 | AAC : | ATC (| GAG (| GAC | GGC i | AGC (| GTG (| CAG | CTC | GCC | 960 250 |

| | | | | | | | | | | 251 | | | | | | | |
|----|------------|------------|-------------------|---------------------|------------------------|-------------------------------|-----------------------|---------------------|------|-----------|------------|-----------|------------|-----|-----|------------|------|
| | Asn 305 | Phe | Lys | Ile | Arg | His 310 | Asn | Ile | Glu | Asp | Gly 315 | Ser | Val | Gln | Leu | Ala 320 | |
| 5 | | | | | | | | | | | GAC Asp | | | | | | 1008 |
| 10 | | | | | | | | | | | GCC Ala | | | | | | 1056 |
| 15 | | | | | | | | | | | GAG Glu | | | | | | 1104 |
| 10 | | | | | | ATG Met | | | | | AAG Lys | TAA | | | | | 1140 |
| 20 | | | (2) | IN) | FORM | ATIOI | v FOI | R SE(| Q ID | NO: | 129: | | | | | | |
| 25 | | (: | (A) (B) (C) | LENG TYPI STR | GTH: E: ar ANDEI | CHARA 379 mino DNESS | amin acio S: s: | no ao i ingle | cids | | | | | | | | |
| 30 | | (1 | v) FI | RAGMI | ENT : | TYPI IYPE DESC | : int | terna | al | מד ה | NO:1 | 129: | | | | | |
| 35 | 1 | Asp | His | Tyr | Asp 5 | Ser | Gln | Gln | Thr | Asn 10 | Asp | Tyr | | | 15 | | |
| | | _ | _ | 20 | _ | _ | | | 25 | _ | Pro | | _ | 30 | - | | |
| 40 | Gly | Thr 50 | 35 Gln | Ile | Glu | Asn | Ile 55 | 40 Glu | Glu | Asp | Phe | Arg 60 | 45 Asp | Gly | Leu | Lys | |
| | Leu 65 | | Leu | Leu | Leu | Glu 70 | | Ile | Ser | Gly | Glu 75 | | Leu | Ala | Lys | Pro 80 | |
| 45 | | | | | 85 | | | | | 90 | Ser Leu | | | | 95 | | |
| | | | Ile | 100 | | | | | 105 | | Thr | | | 110 | | | |
| 50 | Thr | Ile 130 | 115 Ile | Leu | Arg | Arg | Asp 135 | 120 Pro | Pro | Val | Ala | Thr | 125 Met | Val | Ser | Lys | |
| | 145 | Glu | | | | 150 | Gly | | | | Ile 155 | Leu | | | | 160 | |
| 55 | _ | _ | | | 165 | | - | | | 170 | Ser Phe | _ | | _ | 175 | - | |
| | | | | | | | | | | - | | | - | | | | 0.5 |

| | | | | | | | | | | 202 | | | | | | | |
|----|----------------|--------------|----------------|---------------|---------------|---------------|---------------|-------|-----------|----------------|--------------|-------|--------------|----------|------|------------|-----|
| | T 1 10 | | _ | 180 | | | | | 185 | i | | | | 190 |) | | |
| | | | | | | | | 201 | , | | | | 205 | Thr | Туг | Gly | |
| 5 | | Gln 210 | | | | | ~15 | | | | | 220 | Gln | His | | | |
| | Phe 225 | Lys | Ser | Ala | Met | Pro 230 | Glu | Gly | Tyr | Val | Gln | Glu | Arg | Thr | Ile | | |
| | Phe | Lys | Asp | Asp | Gly | Asn | | Lys | Thr | Arg | 235 Ala | Glu | Val | Lys | Phe | 240 Glu | |
| 10 | | Asp | | | Val | | | | Glu | 250 | | | | | | | |
| | | Asp | | 200 | | | | His | Lys | | | | | 222 | | | |
| 15 | | Asn 290 | | | | | Ala | 28U | | | | Asn | 205 | | | | |
| | | Phe | | | | His | 233 | | | | | 200 | | | | | |
| | | His | | | Gln | 210 | | | | | 215 | | | | | | |
| 20 | | Asp | | His | 323 | | | | | 4 3 N | | | | | | | |
| | | Glu | | 240 | | | | | 445 | | | | | 250 | | | |
| | | Ile | | | | | | 3011 | | | | | 365 | 1111 | AIG | AIG | |
| 25 | | 370 | | | • | | 375 | | Deu | 171 | цуѕ | | | | | | |
| | | | (2) | INF | ORMA | TION | FOR | SEC | DI | NO:1 | 30: | | | | | | |
| 30 | | (i |) SE | QUEN | CE C | HARA | CTER | ISTI | CS: | | | | | | | | |
| 30 | | | (B) | TYPE | TH: : nu | clei | c ac | id | | | | | | | | | |
| | | | (C) ; (D) ' | STRA TOPO | NDED: LOGY | NESS : li: | : si: near | ngle | | | | | | | | | |
| 35 | | (ii | i) Mo | O L EC | ULE : | TYPE | : cDi | NA | | | | | | | | | |
| | | (i) | c) FI | EATU | RE: | | | • | | | | | | | | | |
| | | | (A) | NAMI | YTION | ۲: Co | oding | g Se | quen | ce | | | | | | | |
| 40 | | | (D) | отн | ER IN | FORN | ATIC | ON: | | | | | | | | | |
| | | (xi |) SE | QUEN | ICE I | ESCF | RIPTI | ON: | SEQ | ID 1 | NO:13 | 30: | | | | | |
| | ATG O | TG A | GC A | AG G | GC G | AG G | ag c | מיני: | רידירי זי | \CC (| | ma c | ma - | 100 - | me - | - | |
| 45 | Met V 1 | al S | er L | ys G | ly G 5 | lu G | lu I | eu I | ne T | hr (| 3ly V | al V | al P | ro I | TC (| ETG Leu | 48 |
| | | | | | • | | | | 1 | .0 | | | | 1 | .5 | | |
| 50 | GTC G Val G | lu L | | Sp G | ly A | sp V | al A | sn C | GC C | CAC A lis L | AG I ys P | TC A | GC G er V | TG Tal S | CC C | GC ly | 96 |
| - | | | | • | | | | 2 | 5 | | | | 3 | 0 | | | |
| | GAG G Glu G | GC G ly G | AG G lu G | GC G ly A | AT G sp A | CC A la T | CC T hr T | AC G | GC A | AG C | TG A | CC C | TG A | AG T | TC A | TC | 144 |
| 55 | | - | | | | | 4 | U | | | | 4 | 5 | | | | |
| | TGC A | CC A | CC G | GC A | AG C | TG C | CC G | TG C | CC T | GG C | CC A | CC C' | TC G | TG A | CC A | CC | 192 |
| | | | | | | | | | | | | | | | | | 252 |

| | | | | | | | | | | 253 | | | | | | | |
|----|-----|-----------|-----|-----|-------------------|-----|-----------|-----|-----|-----|-----|-----------|-----|-----|-----|-----|-----|
| | Cys | Thr 50 | Thr | Gly | Lys | Leu | Pro 55 | Val | Pro | Trp | Pro | Thr 60 | Leu | Val | Thr | Thr | |
| 5 | | | | | GTG Val | | | | | | | | | | | | 240 |
| 10 | | | | | TTC Phe 85 | | | | | | | | | | | | 288 |
| 15 | | | | | TTC Phe | | | | | | | | | | | _ | 336 |
| .0 | | | | | GGC Gly | | | | | | | | | | | | 384 |
| 20 | | | | | GAG Glu | | | | | | | | | | | | 432 |
| 25 | | | | | CAC His | | | | | | | | | | | | 480 |
| 30 | | | | | AAC Asn 165 | | | | | | | | | | | | 528 |
| 35 | | | | | GAC Asp | | | | | | | | | | | | 576 |
| 33 | | | | | CCC Pro | | | | | | | | | | | | 624 |
| 40 | | | | | AAC Asn | _ | | | | | | | | | | _ | 672 |
| 45 | | | | | GGG Gly | | | | | | | | | | | | 720 |
| 50 | | | | | CGA Arg 245 | | | | | | | | | | | | 768 |
| 55 | | | | | GCC Ala | | | | | | | | | | | | 816 |
| 55 | GAG | CTT | GAC | TTC | TCC | ATC | CTC | TTC | GAC | TAT | GAG | TAT | TTG | AAT | CCG | AAC | 864 |

| | | | | | | | | | | 254 | | | | | | | |
|----|-------------------|--------------------|-----------------------|-----------------------|---------------------|-----------------------|-----------------------|-------------------|-------------------|-------------------------------|-----------------------|--------------------|-------------------|-------------------|-------------------|-----------------------|---------------------|
| | Gl | u Le | u As 27 | p Ph | e Se | r Ile | e Le≀ | 28 | e As | р Ту | r Gl | и Ту | r Le 28 | | n Pr | o Asn | |
| 5 | GA: | A GA u Gl 29 | u GI | G CC u Pr | G AA' o Asi | T GC# n Ala | A CAT A His 295 | 5 Lys | G GTG S Va | C GC | C AG a Se | C CC r Pr 30 | o Pr | C TC | C GG C Gl | A CCC y Pro | 912 |
| 10 | GC/ A1a 305 | ı ıy | C CC r Pr | C GA | T GA' | r GTA P Val 310 | . Met | GA(| TAT | r GGG | C CTO y Let 319 | u Ly | G CCI | А ТА(э Туз | C AGG | C CCC r Pro 320 | 960 |
| 15 | CTT Let | GC Ala | T AG' a Se: | T CTO | TCT 1 Se1 325 | GIY | GAG Glu | CCC Pro | C CCC | GG(Gl _y 330 | Arg | A TTO | C GG# ∈ Gly | A GAC | CCC Pro | G GAT | 1008 |
| | AGC Arg | GT/ Val | A GGG | G CCC Y Pro 340 | GIR | AAG Lys | TTT | CTG Leu | AGC Ser 345 | Ala | GCC Ala | C AAC | G CCA | GCA Ala 350 | Gly | G GCC / Ala | 1056 |
| 20 | TCG Ser | GG(| C CTC / Let 355 | ı ser | C CCT | CGG Arg | ATC Ile | GAG Glu 360 | Ile | ACT Thr | CCC Pro | TCC Ser | CAC His | Glu | CTC Leu | ATC Ile | 1104 |
| 25 | CAG Gln | GCA Ala 370 | r var | GGG Gly | CCC Pro | CTC Leu | CGC Arg 375 | ATG Met | AGA Arg | GAC Asp | GCG Ala | GGC Gly 380 | Leu | CTG Leu | GTG Val | GAG Glu | 1152 |
| 30 | CAG Gln 385 | CCT Pro | CCC Pro | CTG Leu | GCC Ala | GGG Gly 390 | GTG Val | GCC Ala | GCC Ala | AGC Ser | CCG Pro 395 | AGG Arg | TTC Phe | ACC Thr | CTG Leu | CCC Pro 400 | 1200 |
| 35 | GTG Val | CCC | GGC | TTC Phe | GAG Glu 405 | GGC Gly | TAC Tyr | CGC Arg | GAG Glu | CCG Pro 410 | CTT Leu | TGC Cys | TTG Leu | AGC Ser | CCC Pro 415 | GCT Ala | 1248 |
| | AGC Ser | AGC Ser | GGC Gly | TCC Ser 420 | TCT Ser | GCC Ala | AGC Ser | TTC Phe | ATT Ile 425 | TCT Ser | GAC Asp | ACC Thr | TTC Phe | TCC Ser 430 | CCC Pro | TAC Tyr | 1296 |
| 40 | ACC Thr | TCG Ser | CCC Pro 435 | TGC Cys | GTC Val | TCG Ser | CCC Pro | AAT Asn 440 | AAC Asn | GGC Gly | GGG Gly | CCC Pro | GAC Asp 445 | GAC Asp | CTG Leu | TGT Cys | 1344 |
| 45 | CCG Pro | CAG Gln 450 | TTT Phe | CAA Gln | AAC Asn | ATC Ile | CCT Pro 455 | GCT Ala | CAT His | TAT Tyr | TCC Ser | CCC Pro 460 | AGA Arg | ACC Thr | TCG Ser | CCA Pro | 1392 |
| 50 | ATA Ile 465 | ATG Met | TCA Ser | CCT Pro | CGA Arg | ACC Thr 470 | AGC Ser | CTC Leu | GCC Ala | GAG Glu | GAC Asp 475 | AGC Ser | TGC Cys | CTG Leu | GGC Gly | CGC Arg 480 | 1440 |
| 55 | CAC His | TCG Ser | CCC Pro | GTG Val | CCC Pro 485 | CGT (| CCG (Pro) | GCC Ala | Ser | CGC Arg 490 | TCC Ser | TCA Ser | TCG Ser | Pro | GGT Gly 495 | GCC Ala | 1488 |
| | AAG | CGG | AGG | CAT | TCG | TGC (| GCC (| GAG (| GCC | TTG | GTT | GCC | CTG | CCG | ccc | GGA | 153 <i>6</i> 254 |

| | | | | | | | | | | 255 | | | | | | | |
|------------|-----|-----|-----|------------|-------------------|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|------|
| | ГÀЗ | Arg | Arg | His 500 | Ser | Cys | Ala | Glu | Ala 505 | Leu | Val | Ala | Leu | Pro 510 | Pro | Gly | |
| 5 | | | | | CGC Arg | | | | | | | | | | | | 1584 |
| 10 | | | | | GAC Asp | | | | | | | | | | | | 1632 |
| 45 | | | | | ATC Ile | | | | | | | | | | | | 1680 |
| 15 | | | _ | _ | CCC Pro 565 | | | | | | | | | | | | 1728 |
| 20 | | | | | GCC Ala | | | | | | | | | | | | 1776 |
| 25 | | _ | | _ | TTC Phe | | _ | | | | | | | | | | 1824 |
| 30 | | | | | TCC Ser | | | | | | | | | | | | 1872 |
| | | | | | ATT Ile | | | | | | | | | | | | 1920 |
| 35 | | | | | TGG Trp 645 | | | | | | | | | | | | 1968 |
| 40 | | | | | CAG Gln | | | | | | | | | | | | 2016 |
| 45 | | | | | GGG Gly | | | | | | | | | | | | 2064 |
| 50 | | | | | GGC Gly | | | | | | | | | | | | 2112 |
| 5 5 | | | | | GCT Ala | | | | | | | | | | | | 2160 |
| 55 | CAG | GTG | CAC | CGA | ATC | ACG | GGG | AAA | ACT | GTC | ACC | ACC | ACC | AGC | TAT | GAG | 2208 |

| | | | | | | | | | | 256 | | | | | | | |
|-----------|-------|-------|------------|------------|-------|-------|------------|------------|--------------|--------------|-------|---------|------------|--------------|------------|----------|--------|
| | Gln | ı Val | l His | s Arg | 725 | e Thi | r Gly | / Lys | Thr | 730 | | Thi | Thi | r Sei | 735 | Glu 5 | |
| | AAG | ATA | A GTO | G GG | C AAC | C ACC | CAAA | A GTO | CTC | GAG | ATC | . cc | : TTC | GAC | ; ccc | C AAA | 2256 |
| 5 | Lys | Ile | e Val | 740 | / Asr | 1 Thi | Lys | val | . Leu 745 | ı Glu | ı Ile | Pro | Let | 750 | Pro | Lys | 2230 |
| | AAC | AAC | ATO | AGG | GCA | ACC | ATC | GAC | TG1 | GCG | GGG | ATO | TTO | AAC | CTI | AGA | 2304 |
| 40 | Asn | Asn | ı Met | . Arg | g Ala | Thr | Ile | Asp | Суз | Ala | Gly | Ile | Lev | Lys | Leu | Arg | 2304 |
| 10 | | | 755 | • | | | | 760 | | | | | 765 | 5 | | AAG | |
| | Asn | Ala | Asp | Ile | Glu | Leu | Arg | Lvs | Glv | GAG | Thr | GAC | ATI | GGA | AGA | AAG | 2352 |
| 45 | | 770 | | | | | 775 | | 1 | | | 780 | | . Gly | Arg | гур | |
| 15 | אמר | ΔCG | CGG | e cerc | י אכא | CTC | Comm | , mma | | | | | | | | | |
| | Asn | Thr | Arq | Val | Ara | Leu | GTT Val | Phe | Ara | . GTT Val | CAC | ATC | CCA | GAG | TCC | AGT | 2400 |
| | 785 | | | | | 790 | | | | | 795 | | | | | 800 | |
| 20 | GGC | AGA | ATC | GTC | TCT | TTA | CAG | ACT | GCA | TCT | AAC | CCC | ATC | GAG | TGC | TCC | 2448 |
| | GIY | Arg | ше | vai | 805 | | Gln | Thr | Ala | Ser 810 | Asn | Pro | Ile | Glu | Cys 815 | Ser | |
| 0.5 | CAG | CGA | TCT | GCT | CAC | GAG | CTG | CCC | ATG | GTT | GAA | AGA | CAA | GAC | ACA | GAC | 2496 |
| 25 | Gln | Arg | Ser | Ala 820 | His | Glu | Leu | Pro | Met 825 | Val | Glu | Arg | Gln | Asp 830 | Thr | Asp | |
| | AGC | TGC | CTG | GTC | TAT | GGC | GGC | CAG | CAA | ATG | ATC | CTC | ACG | GGG | CAG | ልልሮ | 2544 |
| 30 | Ser | Суѕ | Leu 835 | Val | Tyr | Gly | Gly | Gln 840 | Gln | Met | Ile | Leu | Thr 845 | Gly | Gln | Asn | 2344 |
| | TTT | ACA | TCC | GAG | TCC | AAA | GTT | GTG | TTT | ACT | GAG | AAG | ACC | ልሮል | CAT | CCA | 2592 |
| | Phe | Thr | Ser | Glu | Ser | Lys | Val | Val | Phe | Thr | Glu | Lys | Thr | Thr | Asp | Glv | 2592 |
| 35 | | 850 | | | | | 855 | | | | | 860 | | | - | - | |
| 55 | CAG | CAA | ATT | TGG | GAG | λтс | GAA | ccc | 7.00 | ama. | ~~ m | | | | | | |
| | Gln | Gln | Ile | Trp | Glu | Met | Glu | Ala | Thr | Val | Asn | LVS | Agn | AAG | AGC | CAG | 2640 |
| | 865 | | | | | 870 | | | | | 875 | -,5 | 1100 | Д у 5 | 561 | 880 | |
| 40 | CCC | AAC | ATG | CTT | TTT | GTT | GAG | ATC | CCT | GAA | тат | CGG | אאכ | AAG | CAT | ስጥሮ | 2688 |
| | Pro | Asn | Met | Leu | Pne | Val | Glu | Ile | Pro | Glu | Tyr | Arg | Asn | Lys | His | Ile | . 2000 |
| | | | | | 885 | | | | | 890 | | | | - | 895 | | |
| | CGC | ACA | CCT | GTA | AAA | GTG | AAC | TTC | TAC | GTC | ATC | דעע | GGG | አአር | אמא | 777 | 2736 |
| 45 | Arg | Thr | Pro | Val | Lys | Val | Asn | Phe | Tyr | Val | Ile | Asn | Gly | Lys | Arq | Lvs | 2736 |
| | | | | 900 | | | | | 905 | | | | - | 910 | | 4 - | |
| | CGA | AGT | CAG | CCT | CAG | CAC | TTT | ACC | тас | CAC | CCA | GTC | CCA | ccc | እጥረ | 220 | 2704 |
| | Arg | Ser | Gln | Pro | Gln | His | Phe | Thr | Tyr | His | Pro | Val | Pro | Ala | Ile | LVS | 2784 |
| 50 | | | 915 | | | | | 920 | - | | | | 925 | | | 2,0 | |
| | ACG | GAG | CCC | ACG | GAT | GAA | тдт | GAC | CCC | አ Cm | CTC. | א תריכי | maa | | | | |
| | Thr | Glu | Pro | Thr | Asp | Glu | Tyr | Asp | Pro | Thr | Leu | AIC | TGC | AGC | CCC | ACC | 2832 |
| 55 | | 930 | | | - | | 935 | • | - | | | 940 | -,5 | JC1 | -10 | **** | |
| 55 | ሮልጥ 4 | GGA | ccc | ርሞር | GGG | מממ | CD C | | | | | | | | | | |
| | CAT | JOA | 330 | -10 | 330 | AUC | CAG | CCT | TAC | TAC | CCC | CAG | CAC | CCG | ATG | GTG | 2880 |
| | | | | | | | | | | | | | | | | | 256 |

| | His 945 | Gly | Gly | Leu | Gly | Ser 950 | Gln | Pro | Tyr | Tyr | Pro 955 | Gln | His | Pro | Met | Val 960 | |
|----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|--------------------|-----|------------|-------------|
| 5 | | | | | | | | | | | | | | TGC Cys | | | 2928 |
| 10 | | | | | | | | | | | | | | CAA Gln 990 | | | 2976 |
| 45 | | | | | | | Gln | | | | | Leu | | CCC Pro | | | 3024 |
| 15 | Leu | | | | | Pro | | | | | Ala | | | TCC Ser | | | 3072 |
| 20 | | | | | Ser | | | | | Ala | | | | GGC Gly | Gln | | 3120 |
| 25 | | | | Leu | | | | | Thr | | | | | TCG Ser | | | 3168 |
| 30 | | | Tyr | | | | | Gln | | | | | Gly | AGC Ser 1070 | | | 3216 |
| | | Phe | | | | | Tyr | | | | | Ala | | GGC Gly | _ | | 3264 |
| 35 | Arg | | | | | Pro | | | | | Gln | | | AGC Ser | | | 3312 |
| 40 | | | | | Val | | | | | Asn | | | | CAA Gln | Arg | _ | 3360 |
| 45 | | | | Gly | | | | | Asp | | | | | TTA Leu | | | 3408 |
| 50 | | | Thr | | | | | Gln | | | | | Thr | TAC Tyr 1150 | | | 3456 |
| | | Val | | | | | Arg | | | | | Gly | | CCT Pro | | | 3504 |
| 55 | AAT | CAG | ACG | TAA | | | | | | | | | | | | | 3516 257 |

Asn Gln Thr

```
5 (2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1171 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
```

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

| | 305 | | | | | 310 | | | | | 315 | | | | | 320 |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Leu | Ala | Ser | Leu | Ser 325 | Gly | Glu | Pro | Pro | Gly 330 | Arg | Phe | Gly | Glu | Pro 335 | Asp |
| 5 | Arg | Val | Gly | Pro 340 | | Lys | Phe | Leu | Ser 345 | | Ala | Lys | Pro | Ala 350 | | Ala |
| Ü | Ser | Gly | | | Pro | Arg | Ile | Glu 360 | | Thr | Pro | Ser | | Glu | Leu | Ile |
| | Gln | | 355 Val | Gly | Pro | Leu | _ | | Arg | Asp | Ala | _ | 365 Leu | Leu | Val | Glu |
| 10 | | 370 Pro | Pro | Leu | Ala | _ | 375 Val | Ala | Ala | Ser | | 380 Arg | Phe | Thr | Leu | |
| | 385 Val | Pro | Gly | Phe | Glu | 390 Gly | Tyr | Arg | Glu | Pro | 395 Leu | Cys | Leu | Ser | Pro | 400 Ala |
| | Ser | Ser | Gly | Ser | 405 Ser | Ala | Ser | Phe | Ile | 410 Ser | Asp | Thr | Phe | Ser | 415 Pro | Tyr |
| 15 | | | _ | 420 | | | | | 425 | | _ | | | 430 Asp | | |
| | | | 435 | _ | | | | 440 | | _ | | | 445 | _ | | _ |
| 20 | | 450 | | | | | 455 | | | _ | | 460 | _ | Thr | | |
| 20 | 465 | | | | _ | 470 | | | | | 475 | | _ | Leu | _ | 480 |
| | His | Ser | Pro | Val | Pro 485 | Arg | Pro | Ala | Ser | Arg 490 | Ser | Ser | Ser | Pro | Gly 495 | Ala |
| 25 | Lys | Arg | Arg | His 500 | Ser | Cys | Ala | Glu | Ala 505 | Leu | Val | Ala | Leu | Pro 510 | Pro | Gly |
| | Ala | Ser | Pro 515 | Gln | Arg | Ser | Arg | Ser 520 | Pro | Ser | Pro | Gln | Pro 525 | Ser | Ser | His |
| | Val | Ala 530 | Pro | Gln | Asp | His | Gly 535 | Ser | Pro | Ala | Gly | Tyr 540 | Pro | Pro | Val | Ala |
| 30 | Gly 545 | | Ala | Val | Ile | Met 550 | | Ala | Leu | Asn | Ser 555 | | Ala | Thr | Asp | Ser 560 |
| | | Cys | Gly | Ile | | | Lys | Met | Trp | - | | Ser | Pro | Asp | | |
| | Pro | Val | Ser | | 565 Ala | Pro | Ser | Lys | Ala | 570 Gly | Leu | Pro | Arg | His | 575 Ile | Tyr |
| 35 | Pro | Ala | Val | 580 Glu | Phe | Leu | Gly | Pro | 585 Cys | Glu | Gln | Gly | Glu | 590 Arg | Arg | Asn |
| | Ser | Ala | 595 Pro | Glu | Ser | Ile | Leu | 600 Leu | Val | Pro | Pro | Thr | 605 Trp | Pro | Lys | Pro |
| 40 | Leu | 610 Val | Pro | Ala | Ile | Pro | 615 Ile | Cys | Ser | Ile | Pro | 620 Val | Thr | Ala | Ser | Leu |
| | 625 | | | | | 630 | | _ | | | 635 | | | Tyr | | 640 |
| | | | | | 645 | | | | | 650 | | - | | Tyr | 655 | |
| 45 | | | | 660 | | | | | 665 | | | | | 670 | | |
| | | • | 675 | _ | _ | | | 680 | | | | • | 685 | | | Val |
| | | 690 | | | - | - | 695 | | | - | | 700 | - | Leu | | |
| 50 | Phe 705 | Ile | Gly | Thr | Ala | Asp 710 | Glu | Arg | Ile | Leu | Lys 715 | Pro | His | Ala | Phe | Tyr 720 |
| | Gln | Val | His | Arg | Ile 725 | Thr | Gly | Lys | Thr | Val 730 | Thr | Thr | Thr | Ser | Tyr 735 | Glu |
| 55 | Lys | Ile | Val | Gly 740 | Asn | Thr | Lys | Val | Leu 745 | | Ile | Pro | Leu | Glu 750 | Pro | Lys |
| | Asn | Asn | Met | | Ala | Thr | Ile | Asp | | Ala | Gly | Ile | Leu | Lys | Leu | Arg |

260

| | | | | _ | | | | | | | | | | | | |
|----|------------|--------------|------------|--------------|------------|------------|------------|------------|------------|------------|-------------|------------|-------------|--------------|------------|------------|
| | 7.00 | N 7 - | 755 | | | | | 760 |) | | | | 765 | 5 | | |
| | | ,,, | , | | | | 775 | | | | | 700 | | | | Lys |
| 5 | | | | | | 790 | | | | | 795 | Ile | Pro | | | Ser |
| | Gly | Arg | Ile | Val | Ser 805 | Leu | Gln | Thr | Ala | Ser 810 | Asn | Pro | Ile | Glu | | 800 Ser |
| | Gln | Arg | Ser | Ala 820 | His | | Leu | Pro | Met 825 | Val | Glu | Arg | Gln | | | Asp |
| 10 | Ser | Cys | Leu 835 | Val | Tyr | Gly | Gly | Gln 840 | Gln | Met | Ile | Leu | | | Gln | Asn |
| | Phe | Thr 850 | Ser | | Ser | Lys | Val | Val | Phe | Thr | Glu | | 845 Thr | Thr | Asp | Gly |
| 15 | Gln 865 | | | Trp | Glu | Met 870 | 855 Glu | Ala | Thr | Val | Asp | 860 Lys | Asp | Lys | Ser | Gln |
| | | Asn | Met | Leu | Phe | | Glu | Ile | Pro | Glu | 875 Tyr | Arg | Asn | Lys | His | 880 Ile |
| | Arg | Thr | Pro | Val 900 | Lys | Val | Asn | Phe | Tyr | 890 Val | Ile | Asn | Gly | Lys | 895 Arg | Lys |
| 20 | | | | Pro | Gln | | | Thr | 905 | | | | | 910 | | |
| | Thr | Glu | | | Asp | Glu | Tyr | 920 Asp | Pro | Thr | Leu | Ile | 925 Cys | Ser | Pro | Thr |
| | | 230 | | | Gly | | 935 | | | | | 940 | | | | |
| 25 | 213 | | | | | 950 | | | | | 955 | | | | | 0.60 |
| | Ala | Glu | Ser | Pro | Ser 965 | Сув | Leu | Val | Ala | Thr 970 | Met | Ala | Pro | Cys | Gln 975 | 960 Gln |
| | Phe | Arg | Thr | Gly 980 | Leu | Ser | Ser | Pro | Asp 985 | Ala | Arg | Tyr | Gln | Gln 990 | Gln | Asn |
| 30 | Pro | Ala | Ala 995 | Val | Leu | Tyr | Gln 1 | Arg | Ser | Lys | Ser | | Ser .005 | Pro | Ser | Leu |
| | Leu 1 | Gly 010 | Tyr | Gln | Gln | Pro 1 | Ala 015 | Leu | Met | Ala | | Pro 020 | Leu | Ser | Leu | Ala |
| 35 | Asp . | Ala | His | Arg | Ser 1 | Val 030 | Leu | Val | His | Ala | Gly .035 | Ser | Gln | Gly | | |
| | Ser . | Ala | Leu | Leu | His | Pro | Ser | Pro | Thr | Asn | Gln | Gln | Ala | Ser | Pro | 040 Val |
| | | | | | 045 | | | | 1 | .050 | | | | 7 | A E E | |
| | Ile | | | 000 | | | | 1 | 065 | | | | 1 | 070 | | |
| 40 | Glu : | | 075 | | | | 1 | Cys 080 | Glu | | | 1 | Pro | Gly | | |
| | Arg 1 | Pro 090 | Gly | Pro | Pro : | Pro 1 | Val 095 | Ser | Gln | Gly | Gln . | Arg | Leu | Ser | Pro | Gly |
| 45 | Ser : | Tyr | Pro | Thr | Val : | Ile | Gln | Gln | Gln | Asn | Ala ' | Thr : | Ser | Gln . | Arg . | Ala |
| 45 | 103 | | | | 1. | TTO | | | | 7 | 115 | | | | - | 100 |
| | Ala 1 | | | 1 | 145 | | | | 1 | 130 | | | | 7 | 125 | |
| | Gly V | Val | Thr | Ile : 140 | Lys (| Gln (| Glu (| Gln . | Asn | Leu . | Asp (| 3ln ' | | Tyr : | Leu . | Asp |
| 50 | Asp \ | Val : | Asn (| | Ile : | Ile A | Arg 1 | Lys (| 145 Glu | Phe | Ser (| Glv 1 | 1 Pro | 150 Pro 1 | Ala : | Ara |
| | | | 133 | | | | 1 | 160 | | | ' | | 165 | | | 3 |
| | Asn (| 31n ' 170 | rnr | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO:132:

PCT/DK98/00145 WO 98/45704

| 5 | | (1) | (A) (B) (C) (D) | LENG TYPE STRA TOPO MOLEG | ETH: E: nt ANDEI OLOGY CULE IRE: | CHARF 3546 Iclei DNESS 7: li TYPE | basic ac E: si inear E: cI | se pa cid ingle | airs | ıce | | | | | | | | |
|----|-----------|------------|--------------------------|---------------------------------------|----------------------------------|--|-------------------------------------|-----------------------|------------|-----------|-----------|------------|------------|------------|-----------|-----------|-----|-----|
| | | () | (D) | OTI | HER I | ON: 1 INFOR | (TAMS | ON: | - : SE(|) ID | NO: 1 | 132: | | | | | | |
| 15 | | | | | | CGG Arg | | | | | | | | | | | 48 | |
| 20 | | | | | | GGC Gly | | | | | | | | | | | 96 | |
| 25 | | | | | | TAT Tyr | | | | | | | | | | | 144 | |
| 30 | His | Lys 50 | Val | Ala | Ser | CCA Pro | Pro 55 | Ser | Gly | Pro | Ala | Tyr 60 | Pro | Asp | Asp | Val | 192 | |
| 35 | Met 65 | Asp | Tyr | Gly | Leu | AAG Lys 70 | Pro | Tyr | Ser | Pro | Leu 75 | Ala | Ser | Leu | Ser | Gly 80 | 240 | |
| 40 | Glu | Pro | Pro | Gly | Arg 85 | TTC | Gly | Glu | Pro | Asp 90 | Arg | Val | Gly | Pro | Gln 95 | Lys | 288 | |
| 40 | Phe | Leu | Ser | Ala 100 | Ala | AAG Lys | Pro | Ala | Gly 105 | Ala | Ser | Gly | Leu | Ser 110 | Pro | Arg | 336 | |
| 45 | Ile | Glu | Ile 115 | Thr | Pro | TCC | His | Glu 120 | Leu | Ile | Gln | Ala | Val 125 | Gly | Pro | Leu | 384 | |
| 50 | Arg | Met 130 | Arg | Asp | Ala | | Leu 135 | Leu | Val | Glu | Gln | Pro 140 | Pro | Leu | Ala | Gly | 432 | |
| 55 | | | | | | AGG Arg 150 | | | | | | | | | | | 480 | |
| | TAC | CGC | GAG | CCG | CTT | TGC | TTG | AGC | CCC | GCT | AGC | AGC | GGC | TCC | TCT | GCC | 528 | 261 |

| | Arg | Ser | Pro | Ser | Pro | CAG Gln | Pro | Ser | Ser | Hic | Unl | GCA | CCC | CAG | GAC | CAC | 864 |
|----|------------|------------|-------|------------|-------|------------|----------------|------------|----------------------|--------------|------------|------------|--------------|------------|-------|-----|------|
| 30 | | | 2/5 | | | Gln | | 280 | | | | | 285 | | | | |
| | GGC | TCC | CCG | GCT | GGG | TAC | CCC | CCT | GTG | GCT | GGC | TCT | GCC | GTG | ATC | ATG | 912 |
| | Gly | Ser 290 | Pro | Ala | Gly | Tyr | Pro | Pro | Val | Ala | Gly | Ser | Ala | Val | Ile | Met | 912 |
| 35 | | | | | | | 295 | | | | | 300 | | | | | |
| | GAT | GCC Ala | CTG | AAC | AGC | CTC | GCC | ACG | GAC | TCG | CCT | TGT | GGG | ATC | CCC | CCC | 960 |
| | 305 | Ата | ьeu | Asn | ser | Leu 310 | Ala | Thr | Asp | Ser | Pro 315 | Сув | Gly | Ile | Pro | Pro | |
| 40 | አለር | איייט | maa | | | | | | | | | | | | | 320 | |
| 70 | Lys | Met | Trp | Lys | Thr | AGC Ser | CCT Pro | GAC Asp | CCC Pro | TCG Ser | CCG Pro | GTG Val | TCT | GCC Ala | GCC | CCA | 1008 |
| | | | | | 325 | | | | | 330 | 110 | vuı | DCI | | 335 | PIO | |
| | TCC | AAG | GCC | GGC | CTG | CCT | CGC | CAC | ATC | TAC | CCG | GCC | GTG | GAG | ייירי | ርጥር | 1056 |
| 45 | Ser | Lys | Ala | Gly 340 | Leu | Pro | Arg | His | Ile | Tyr | Pro | Ala | Val | Glu | Phe | Leu | 1056 |
| | | | | | | | | | 345 | | | | | 350 | | | |
| | GGG Glv | CCC | TGC | GAG | CAG | GGC | GAG . | AGG | AGA | AAC | TCG | GCT | CCA | GAA | TCC | ATC | 1104 |
| 50 | Gly | - 10 | 355 | GIU | GIII | GIY | GIU. | Arg 360 | Arg . | Asn . | Ser | | Pro 365 | Glu . | Ser | Ile | |
| | CTG | СТС | ርጥጥ | ccc | ccc | א כיוחי | TO C | aa~ | | | | | | | | | |
| | CTG Leu | Leu | Val | Pro | Pro | ACT ' | rgg (Trp] | CCC Pro | AAG Lvs | CCG (Pro | CTG Leu | GTG (| CCT (| GCC A | ATT | CCC | 1152 |
| 55 | | 370 | | | | | 375 | | -,- | | | 380 | | nia . | - T E | FIO | |
| 55 | ATC | TGC | AGC . | ATC | CCA (| GTG : | ACT 1 | מטפ | ፐ ሮሮ <i>'</i> | مىلات ب | יייטיטי | CC2 - | ~mm · | 73.C | na.~ | | |
| | | | | - | | | | JUA | | -10 | -C1 | CCA (| ~1.I. (| SAG | r.GG | CCG | 1200 |
| | | | | | | | | | | | | | | | | | 262 |

| | | | | | | | | | | 263 | | | | | | | |
|-----|------------|-----|-----|-----|-------------------|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|------|
| | Ile 385 | Cys | Ser | Ile | Pro | Val 390 | Thr | Ala | Ser | Leu | Pro 395 | Pro | Leu | Glu | Trp | Pro 400 | |
| 5 | | | | | TCA Ser 405 | | | | | | | | | | | | 1248 |
| 10 | | | _ | | CGG Arg | | | | | | | | | | | | 1296 |
| 45 | | | | | ACT Thr | | | | | | | | | | | | 1344 |
| 15 | | | | | CCT Pro | | | | | | | | | | | | 1392 |
| 20 | _ | | | | AAG Lys | | | | | | | | | | | | 1440 |
| 25 | | | | | ACC Thr 485 | | | | | | | | | | | | 1488 |
| 30 | | | | | ATC Ile | | | | | | | | | | | | 1536 |
| 0.5 | | | | | GGG Gly | | | | | | | | | | | | 1584 |
| 35 | | | | | ACG Thr | | | | | | | | | | | | 1632 |
| 40 | | | | | CAC His | | | | | | | | | | | | 1680 |
| 45 | | | | | AAC Asn 565 | | | | | | | | | | | | 1728 |
| 50 | | | | | GAA Glu | | | | | | | | | | | | 1776 |
| EF | | | | | ATC Ile | | | | | | | | | | | | 1824 |
| 55 | GTT | GTG | TTT | ACT | GAG | AAG | ACC | ACA | GAT | GGA | CAG | CAA | ATT | TGG | GAG | ATG | 1872 |

| | | | | | | | | | | 264 | | | | | | | |
|----|-------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------------|--------------------|
| | Va | 1 Va 63 | al Ph | ne Th | ır Gl | u Ly | s Th 61 | r Th 5 | r As | p Gl | y Gl | n Gl 62 | | e Tr | p Gl | lu Met | |
| 5 | 62 | 5 | .u 11. | ır va | I AS | 63(Б г.У: | s Asj | р гу | s Se | r Gl | n Pr 63 | o As 5 | n Me | t Le | u Ph | CT GTT ie Val 640 | 1920 |
| 10 | | | | o gi | 64: | 5 5 | j ASI | л гу | s His | 65 E | ≥ Arq | g Th | r Pr | o Va | 1 Ly 65 | | 1968 |
| 15 | | | - 19 | 66 | 0 | a ASI | 1 G13 | / Lys | 665 | J Lys | S Arg | g Se: | r Glı | 1 Pro | 9 Gl: | G CAC n His | 2016 |
| | TTT Phe | AC Th | C TA T Ty: | | C CCA | A GTC Val | Pro | GC(Ala 680 | a TTE | AAC Lys | ACC Thr | G GAC | G CCC 1 Pro 685 | Thi | G GA | r GAA p Glu | 2064 |
| 20 | TAT Tyr | GA As _l | , | C ACT | r CTG | ATC | TGC Cys 695 | Ser | C CCC | ACC Thr | CAT | GGZ Gly 700 | / Gly | CTC | GG(| G AGC / Ser | 2112 |
| 25 | CAG Gln 705 | | Г ТАС Э Туз | TAC Tyr | C CCC | CAG Gln 710 | CAC His | CCG Pro | ATG Met | GTG Val | GCC Ala 715 | GAG Glu | TCC Ser | CCC | TCC Ser | TGC Cys 720 | 2160 |
| 30 | CTC Leu | GT(| GCC Ala | ACC Thr | ATG Met 725 | GCT Ala | CCC Pro | TGC Cys | CAG Gln | CAG Gln 730 | TTC Phe | CGC Arg | ACG Thr | GGG Gly | CTC Leu 735 | TCA Ser | 2208 |
| 35 | TCC Ser | CCI Pro | GAC Asp | GCC Ala 740 | CGC Arg | TAC Tyr | CAG Gln | CAA Gln | CAG Gln 745 | AAC Asn | CCA Pro | GCG Ala | GCC Ala | GTA Val 750 | CTC Leu | TAC Tyr | 2256 |
| | CAG Gln | CGG Arg | AGC Ser 755 | AAG Lys | AGC Ser | CTG Leu | AGC Ser | CCC Pro 760 | AGC Ser | CTG Leu | CTG Leu | GGC Gly | TAT Tyr 765 | CAG Gln | CAG Gln | CCG Pro | 2304 |
| 40 | GCC Ala | CTC Leu 770 | ATG Met | GCC Ala | GCC Ala | CCG Pro | CTG Leu 775 | TCC Ser | CTT Leu | GCG Ala | GAC Asp | GCT Ala 780 | CAC His | CGC Arg | TCT Ser | GTG Val | 2352 |
| 45 | CTG Leu 785 | GTG Val | CAC His | GCC Ala | GGC Gly | TCC Ser 790 | CAG Gln | GGC Gly | CAG Gln | Ser | TCA Ser 795 | GCC Ala | CTG Leu | CTC Leu | CAC His | CCC Pro 800 | 2400 |
| 50 | TCT Ser | CCG Pro | ACC Thr | AAC Asn | CAG Gln 805 | CAG (| GCC Ala | TCG Ser | Pro | GTG Val 810 | ATC Ile | CAC His | TAC Tyr | TCA Ser | CCC Pro 815 | ACC Thr | 2448 |
| 55 | AAC Asn | CAG Gln | CAG Gln | CTG Leu 820 | CGC Arg | TGC (Cys (| GGA : | Ser | CAC (His (825 | CAG (Gln (| GAG ' | TTC Phe | Gln | CAC His 830 | ATC Ile | ATG Met | 2496 |
| | TAC ' | TGC | GAG | AAT | TTC | GCA (| CCA (| GGC / | ACC I | ACC I | AGA (| CCT | GGC (| CCG | CCC | CCG | 2544 264 |

| | | | | | | | | | | 265 | | | | | | | |
|-----|-----|--------------------|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----------|
| | Tyr | Cys | Glu 835 | Asn | Phe | Ala | Pro | Gly 840 | Thr | Thr | Arg | Pro | Gly 845 | Pro | Pro | Pro | |
| 5 | | AGT Ser 850 | | | | | | | | | | | | | | | 2592 |
| 10 | | CAG Gln | | | | | | | | | | | | | | | 2640 |
| 15 | | AGT Ser | | | | | | | | | | | | | | | 2688 |
| 15 | | CAG Gln | | | | | | | | | | | | | | | 2736 |
| 20 | | AAG Lys | | | | | | | | | | | | | | | 2784 |
| 25 | | TCG Ser 930 | | | | | | | | | | | | | | | 2832 |
| 30 | | AAG Lys | | | | | | | | | | | | | | | 2880 |
| 0.5 | | GAC Asp | _ | | _ | | | | | | | | | | | | 2928 |
| 35 | | GGC Gly | | | | | | | | | | | | | | | 2976 |
| 40 | | GGC Gly | | | | | Pro | | | | | Val | | | | | 3024 |
| 45 | Tyr | GGC Gly L010 | | | | Phe | | | | | Asp | | | | | | 3072 |
| 50 | | TTC Phe | | | Ser | | | | | Gly | | | | | Arg | | 3120 |
| | | TTC Phe | | ГÀЗ | | | | | Tyr | | | | | Glu | | | 3168 |
| 55 | TTC | GAG | GGC | GAC | ACC | CTG | GTG | AAC | CGC | ATC | GAG | CTG | AAG | GGC | ATC | GAC | 3216 2 |

| | 266 | |
|----|--|------|
| | Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp 1060 1065 1070 | |
| 5 | TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC AAC TAC Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr 1075 1080 1085 | 3264 |
| 10 | AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC GGC ATC Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile 1090 1095 1100 | 3312 |
| 15 | AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GTG CAG Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln 1105 1110 1115 1120 | 3360 |
| | CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC CCC GTG Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val 1125 1130 1135 | 3408 |
| 20 | CTG CTG CCC GAC AAC CAC TAC CTG AGC ACC CAG TCC GCC CTG AGC AAA Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys 1140 1145 1150 | 3456 |
| 25 | GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC GTG ACC Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr 1155 1160 1165 | 3504 |
| 30 | GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 1170 1180 | 3546 |
| 35 | (2) INFORMATION FOR SEQ ID NO:133: (i) SEQUENCE CHARACTERISTICS: | |
| 40 | (A) LENGTH: 1181 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal | |
| 45 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:133: | |
| | Met Asn Ala Pro Glu Arg Gln Pro Gln Pro Asp Gly Gly Asp Ala Pro 1 5 10 15 Gly His Glu Pro Gly Gly Ser Pro Gln Asp Glu Leu Asp Phe Ser Ile 20 25 | |
| 50 | Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn Glu Glu Glu Pro Asn Ala 35 40 45 His Lys Val Ala Ser Pro Pro Ser Gly Pro Ala Tyr Pro Asp Asp Val | |
| 55 | Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro Leu Ala Ser Leu Ser Gly | |
| | Glu Pro Pro Gly Arg Phe Gly Glu Pro Asp Arg Val Gly Pro Gln Lys | |

| | D1 | • | a | | 85 | - | _ | | | 90 | _ | | | | 95 | |
|------------|-------|------------|----------|------------|------|-----------------|-----|-------|-------------|-------|------------|--------|------------|-------|------------|----------|
| | Pne | ьeu | ser | | Ala | rys | Pro | Ala | | Ala | Ser | Gly | Leu | | Pro | Arg |
| | | | | 100 | _ | _ | | | 105 | | | | | 110 | | |
| _ | lle | GIu | | Thr | Pro | Ser | His | | Leu | Ile | Gln | Ala | | Gly | Pro | Leu |
| 5 | _ | | 115 | _ | | | | 120 | | | | | 125 | | | |
| | Arg | | Arg | Asp | Ala | Gly | | Leu | Val | Glu | Gln | Pro | Pro | Leu | Ala | Gly |
| | | 130 | | | | | 135 | | | | | 140 | | | | |
| | | Ala | Ala | Ser | Pro | | Phe | Thr | Leu | Pro | Val | Pro | Gly | Phe | Glu | Gly |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| 10 | Tyr | Arg | Glu | Pro | | Суѕ | Leu | Ser | Pro | | Ser | Ser | Gly | Ser | Ser | Ala |
| | | | | | 165 | | | | | 170 | | | | | 175 | |
| | ser | Phe | Ile | | Asp | Thr | Phe | Ser | | Tyr | Thr | Ser | Pro | | Val | Ser |
| | _ | | _ | 180 | | | | | 185 | | | | | 190 | | |
| 4 == | Pro | Asn | | GIA | GIA | Pro | Asp | | Leu | Cys | Pro | Gln | Phe | Gln | Asn | Ile |
| 15 | | | 195 | | | _ | | 200 | | | | | 205 | | | |
| | Pro | | His | Tyr | Ser | Pro | | Thr | Ser | Pro | Ile | Met | Ser | Pro | Arg | Thr |
| | ^ | 210 | | | | | 215 | | | | | 220 | | | | |
| | | Leu | Ala | Glu | Asp | | Сув | Leu | Gly | Arg | | Ser | Pro | Val | Pro | |
| 00 | 225 | | _ | _ | _ | 230 | | | | | 235 | | | | | 240 |
| 20 | Pro | Ата | ser | Arg | | ser | Ser | Pro | GIA | | Lys | Arg | Arg | His | | Cys |
| | | ~ 3 | | . | 245 | | | _ | _ | 250 | | _ | _ | | 255 | _ |
| | Ala | GIU | Ата | | vai | Ala | Leu | Pro | | GIY | АТа | Ser | Pro | | Arg | Ser |
| | 7 ~~~ | 602 | Dro | 260 | Dwa | ~1 _n | Dwo | | 265 | *** | **- 7 | 77- | | 270 | | *** |
| 25 | Arg | Ser | 275 | 261 | PLO | GIII | PIO | | ser | HIS | vaı | Ala | | GIN | Asp | HIS |
| 20 | Gly | Cor | | ת ז ת | Gly | T-1- | Dro | 280 | 17-1 | n 3 - | <i>α</i> 1 | Ser | 285 | 17. 7 | T1. | Mah |
| | Cry | 290 | 110 | AIG | GIY | T y L | 295 | PIO | vaı | мта | GIA | 300 | Ald | vai | 116 | Mec |
| | Δen | | T.e11 | Aen | Sor | T.011 | | Thr | λcn | Ca* | Dro | Cys | <i>α</i> 1 | T10 | Dro | Dro |
| | 305 | | ac u | 11011 | 001 | 310 | niu | * 111 | тэр | SCI | 315 | Суз | GIY | 116 | FIU | 320 |
| 30 | | Met | Trn | Lvs | Thr | | Pro | Aen | Pro | Ser | | Val | Ser | λla | בומ | |
| | -1- | | | -7- | 325 | | | | | 330 | 110 | V 14.1 | 501 | AIU | 335 | 110 |
| | Ser | Lvs | Ala | Glv | | Pro | Ara | His | Tle | | Pro | Ala | Val | Glu | | Len |
| | | - | | 340 | | | 5 | | 345 | -1- | | | | 350 | | |
| | Gly | Pro | Cvs | Glu | Gln | Glv | Glu | Ara | - | Asn | Ser | Ala | Pro | | Ser | Ile |
| 35 | - | | 355 | | | • | | 360 | | | | | 365 | | | |
| | Leu | Leu | Val | Pro | Pro | Thr | Trp | Pro | Lys | Pro | Leu | Val | | Ala | Ile | Pro |
| | | 370 | | | | | 375 | | • | | | 380 | | | | |
| | Ile | Cys | Ser | Ile | Pro | Val | Thr | Ala | Ser | Leu | Pro | Pro | Leu | Glu | Trp | Pro |
| | 385 | | | | | 390 | | | | | 395 | | | | _ | 400 |
| 40 | Leu | Ser | Ser | Gln | Ser | Gly | Ser | Tyr | Glu | Leu | Arg | Ile | Glu | Val | Gln | Pro |
| | | | | | 405 | | | | | 410 | | | | | 415 | |
| | Lys | Pro | His | His | Arg | Ala | His | Tyr | Glu | Thr | Glu | Gly | Ser | Arg | Gly | Ala |
| | | | | 420 | | | | | 425 | | | | | 430 | | |
| | Val | Lys | Ala | Pro | Thr | Gly | Gly | His | ${\tt Pro}$ | Val | Val | Gln | Leu | His | Gly | Tyr |
| 45 | | | 435 | | | | | 440 | | | | | 445 | | | |
| | Met | | Asn | Lys | Pro | Leu | | Leu | Gln | Ile | Phe | Ile | Gly | Thr | Ala | Asp |
| | _ | 450 | | | | | 455 | | | | | 460 | | | | |
| | | Arg | Ile | Leu | Lys | | His | Ala | Phe | Tyr | Gln | Val | His | Arg | Ile | Thr |
| E 0 | 465 | | m1 | | _, | 470 | | _ | _ | | 475 | | <u>-</u> | | | 480 |
| 50 | GTA | гув | Thr | val | | Thr | Thr | Ser | Tyr | | Lys | Ile | Val | Gly | | Thr |
| | T | 37. 3 | . | ~1 | 485 | _ | _ | ~ 7 | _ | 490 | _ | _ | | | 495 | |
| | гλа | vaı | ьeu | | тте | Pro | Leu | GIu | | ràs | Asn | Asn | Met | | Ala | Thr |
| | Tle | λ ~~ | C110 | 500 31a | G1 | т1 - | T | T | 505 | 7 | D = | 77- | 3 | 510 | a 2 | T |
| 55 | TIE | Asp | 515 | чтя | GTÀ | тте | neu | | ьeu | arg | Asn | Ala | | тте | GIU | ьeu |
| 55 | Ara | Tare | | Glu | Thr | Acn | Tla | 520 | ۸ | T | n | mb~ | 525 | 17-7 | A | T 0 |
| | 9 | -ys | Gry | JIU | TIIL | veħ | 116 | GIA | Arg | пÀв | АЗП | Thr | ALG. | val | Arg | ьeu |

| | | | | | | | | | | | | | 268 | | | | | | | | • |
|----|------------|------------|----------|------|------------|------------|------------|-----|------|------|------------|----------|------|------------|------|----------|------------|------------|------------|----------|------------|
| | | | 530 | | | | | | 53 | 5 | | | | | | 540 | | | | | |
| | V 5 | al 45 | Ph∈ | Ar | g Vá | al H | is : | [le | Pro | o G. | lu s | Ser | Se: | r G | ly A | Arg | 11 | e Va | ıls | er | Leu |
| 5 | G | ln | Thr | Al | a Se | r A 5 | sn 1 65 | Pro | Ile | e G] | lu (| Cys | Se: | r G | ln A | Arg | Se | r Al | a H | is | 560 Glu |
| | L | eu | Pro | Me | t Va 58 | 1 G | lu A | ırg | Glr | n As | p 7 | hr 85 | Ası | Se | er (| 'ys | Let | ı Va | 1 T | 75 yr | Gly |
| 40 | | | | | | | | | | | у (| ln | Asr | | | | | | u S | | Lys |
| 10 | | | | | | | | | | | | | | | | | Ιlε | Tr | | | Met |
| | G. 62 | Lu 2 25 | Ala | Thi | r Va | l As | p L | ys | Asp | Ly | s S | er | Gln | Pr | O A | sn | Met | Le | u Pl | he | Val |
| | | | | | Gl | | | | | | | | | | | | | | | | |
| 15 | | | | | Va: | | | | | | | | | | | | | | | | |
| | | | | | 660 His | | | | | | | | | | | | | | | | |
| 20 | | | | | | | | | | | | | | | | | | | | | |
| | | | | | Thi | | | | | | | | | | | | | | | | |
| | | | | | Туг | | | | | | | | | | | | | | | | |
| 25 | | | | | Thr | | | | | | | | | Phe | e Ar | | | | | | |
| | | | | | Ala 740 | | | | | | | n . | Asn | | | | | | | | |
| 30 | | | | | Lys | | | | | | Se | r | | | | | | | Gl | | |
| 30 | | | | | Ala | | | | | | | | | | | a H | lis | | | | |
| | 785 | 1 V a | 1 L | HIS | Ala | GΤλ | ' Se 79 | r G | ln | Gly | G1 | n s | Ser | Ser | Al | a L | eu | Léu | His | 5 E | ro |
| 35 | Ser | Pı | : 0: | Thr | Asn | Gln 805 | G1: | n A | la | Ser | Pr | 0 V | /al | 795 Ile | Hi | s T | yr | Ser | Pro | 3 I c | 00 hr |
| | | | | | Leu 820 | Arg | Су | | | | | s G | | | | | | | | e M | |
| | | | | | Asn | | | | | | Th | r T | | | | | ly | | | | |
| 40 | | | | | Gly | | | | eu 9 | Ser | | | | | | P | | | | | |
| | 865 | G1 | n G | ln . | Asn | Ala | Thi | S | er (| 3ln | Arg | j A | la A | Ala | Lys | A | sn (| Gly | Pro | P | ro |
| 45 | | | | | Gln | | | | | | | A | la (| | | | | | | | |
| | Glu | | | sn 1 | | | | | | | Let | B. | | | | | | | | | |
| | Arg | Ly | s G 9 | | | Ser | Gly | Pı | co P | ro | 905 Ala | A: | rg A | sn | Gln | Th | ır A |)10 Arg | Ile | Le | eu |
| 50 | Gln | Se: | r T | hr (| /al | Pro | Arg | A] | la A | rg | Asp | Pı | ro P | ro | Val | 92 A1 | :5 .a 1 | hr 1 | Met | Va | al |
| | Ser 945 | | | | | | | Ph | ıe T | | | | | | | 11 | | | | | |
| 55 | Leu | | | | | | Asn | | | | | | ne S | er | | | | | | | |
| | Glu | Gly | As | sp A | la : | Chr | Tyr | Gl | у Ь | ys : | Leu | Th | r L | eu | Lys | Ph | e I | le (| 975 Cys | Th | r |

| | 980 985 990 | |
|----|--|-----|
| | Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr 995 1000 1005 | |
| 5 | Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His 1010 1015 1020 | |
| | Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr | |
| | 025 1030 1035 1040 | |
| | Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys 1045 1050 1055 | |
| 10 | Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp | |
| | 1060 1065 1070 | |
| | Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr | |
| | 1075 1080 1085 | |
| 45 | Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile | |
| 15 | 1090 1095 1100 Luc Val Aca Pho Luc Ilo Aca Hic Aca Ilo Clu Aca Clu Cor Val Cla | |
| | Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln 105 1110 1115 1120 | |
| | Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val | |
| | 1125 1130 1135 | |
| 20 | Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys | |
| | 1140 1145 1150 | |
| | Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr | |
| | 1155 1160 1165 | |
| | Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys | |
| 25 | 1170 1175 1180 | |
| | (2) INFORMATION FOR SEQ ID NO:134: | |
| | (2) INFORMATION FOR BEQ ID NO.134. | |
| | (i) SEQUENCE CHARACTERISTICS: | |
| 30 | (A) LENGTH: 2802 base pairs | |
| | (B) TYPE: nucleic acid | |
| | (C) STRANDEDNESS: single | |
| | (D) TOPOLOGY: linear | |
| | | |
| 35 | (ii) MOLECULE TYPE: cDNA | |
| | (ix) FEATURE: | |
| | (A) NAME/KEY: Coding Sequence | |
| | (B) LOCATION: 12799 | |
| 40 | (D) OTHER INFORMATION: | |
| | (-, | |
| | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:134: | |
| | ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48 | |
| 45 | Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu | |
| | 1 5 10 15 | |
| | | |
| | GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96 | |
| | Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly | |
| 50 | 20 25 30 | |
| | | |
| | GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144 | |
| | Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile | |
| EE | 35 40 45 | |
| 55 | THE ARE ARE COL AND COME OF THE COL THE COL ARE ONE ARE ARE ARE ARE | |
| | TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192 | 200 |
| | • | 269 |

| | _ | , | | | | | | | | 2/0 | | | | | | | |
|----|-------------------|-------------------|-----------------------|---------------------|---------------------|----------------------|-------------------|-------------------|-----------------------|-------------------|----------------------|-------------------|-------------------|-------------------|----------------------|----------------------|------------|
| | Cy | 5 Th | r Th | r Gl | у Lу | s Le | ı Pro | o Va | l Pr | o Tr | p Pro | 0 Th | | u Va | l Th | r Thr | |
| 5 | CT(Let 65 | AC Th | C TA r Ty | C GG r Gl | C GT y Va | G CA0 1 Gl: 70 | TG0 | C TT | C AGo | C CG(| C TAG g Ty: 75 | C CC | C GA | C CA | C AT s Me | G AAG t Lys 80 | 240 |
| 10 | CAC Glr | CAO Hi | C GA | C TT p Ph | C TT e Pho 85 | C AAC | TC(| C GCC | C ATO | CCC Pro | C GAA | A GGG | С ТАС у Туз | C GT | C CA(1 Gl: 95 | G GAG n Glu | 288 |
| 15 | CGC Arg | ACC Thi | C ATO | C TTO Pho 100 | e Pne | C AAG E Lys | GAC Asp | GA(| GGC Gly 105 | Asn | TAC Tyr | Lys | G ACC | C CGC Arg | g Ala | C GAG a Glu | 336 |
| | GTG Val | Lys | F TTC F Phe 115 | - 010 | G GG(| GAC Asp | ACC | CTC Leu 120 | val | AAC Asn | CGC Arg | ATC Ile | GAG Glu 125 | Let | AAC Lys | GGC Gly | 384 |
| 20 | ATC Ile | GAC Asp 130 | PILE | AAC Lys | GAG Glu | GAC Asp | GGC Gly 135 | Asn | : ATC | CTG Leu | GGG Gly | CAC His | Lys | CTG Leu | GAG Glu | TAC | 432 |
| 25 | AAC Asn 145 | TAC | AAC Asn | : AGC | CAC His | AAC Asn 150 | GTC Val | TAT Tyr | ATC Ile | ATG Met | GCC Ala 155 | GAC Asp | AAG Lys | CAG Gln | AAG Lys | AAC Asn 160 | 480 |
| 30 | GGC | ATC Ile | AAG Lys | GTG Val | AAC Asn 165 | TTC Phe | AAG Lys | ATC Ile | CGC Arg | CAC His 170 | AAC Asn | ATC Ile | GAG Glu | GAC Asp | GGC Gly 175 | AGC Ser | 528 |
| 35 | GTG Val | CAG Gln | CTC Leu | GCC Ala 180 | GAC Asp | CAC His | TAC Tyr | CAG Gln | CAG Gln 185 | AAC Asn | ACC Thr | CCC Pro | ATC Ile | GGC Gly 190 | GAC Asp | GGC Gly | 576 |
| | CCC Pro | GTG Val | CTG Leu 195 | CTG Leu | CCC Pro | GAC Asp | AAC Asn | CAC His 200 | TAC Tyr | CTG Leu | AGC Ser | ACC Thr | CAG Gln 205 | TCC Ser | GCC Ala | CTG Leu | 624 |
| 40 | | AAA Lys 210 | GAC Asp | CCC Pro | AAC Asn | GAG Glu | AAG Lys 215 | CGC Arg | GAT Asp | CAC His | Met | GTC Val 220 | CTG Leu | CTG Leu | GAG Glu | TTC Phe | 672 |
| 45 | GTG Val 225 | ACC Thr | GCC Ala | GCC Ala | GGG Gly | ATC Ile 230 | ACT Thr | CTC Leu | GGC Gly | Met | GAC Asp 235 | GAG Glu | CTG Leu | TAC Tyr | AAG Lys | TCC Ser 240 | 720 |
| 50 | GGA Gly | CTC Leu | AGA Arg | TCT Ser | CGA Arg 245 | GGG Gly | AGC Ser | ATG Met | Gly | ACC Thr 250 | TTG Leu | CGG Arg | GAT Asp | TTA Leu | CAG Gln 255 | TAC Tyr | 768 |
| 55 | GCG (| CTC Leu | GIII | GAG Glu 260 | AAG Lys | ATC (| GAG (| GIu | CTG . Leu . 265 | AGG (| CAG (| CGG Arg | Asp | GCT Ala 270 | CTC Leu | ATC Ile | 816 |
| | GAC (| GAG | CTG | GAG | CTG | GAG 1 | fTG (| GAT | CAG Z | AAG (| GAC (| GAA | CTG . | ATC | CAG | AAG | 864 270 |

| | | | | | | | | | | 2/1 | | | | | | | |
|-----|-----|-------------------|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----------|
| | Asp | Glu | Leu 275 | Glu | Leu | Glu | Leu | Asp 280 | Gln | Lys | Asp | Glu | Leu 285 | Ile | Gln | Lys | |
| 5 | | CAG Gln 290 | | | | | | | | | | | | | _ | | 912 |
| 10 | | CAG Gln | | | | _ | | | | | | | | _ | | | 960 |
| 45 | | AAG Lys | | | | | | | | | | | | | _ | | 1008 |
| 15 | | CTC Leu | | | | | | | | | | | | | | | 1056 |
| 20 | | GAT Asp | | | | | | | | | | | | | | | 1104 |
| 25 | | GAG Glu 370 | | | | | | | | | | | | | | _ | 1152 |
| 30 | | TAT Tyr | | | | | | | | | | | | | | | 1200 |
| | | GTG Val | | | | | | | | | | | | | | _ | 1248 |
| 35 | | AAG Lys | | | | | | | | | | | | _ | | _ | 1296 |
| 40 | | CTT Leu | | | | | | | | | _ | | | | _ | | 1344 |
| 45 | | AAA Lys 450 | | | | | | | | | | | | | | | 1392 |
| 50 | | ACA Thr | | | | | | | | | | | | | | | 1440 |
| e e | | CCA Pro | | | | | | | | | | | | | | | 1488 |
| 55 | GAT | GTC | CTT | GAA | GAG | ACC | CAC | TAT | GAA | AAT | GGA | GAA | TAT | ATT | ATC | AGG | 1536 2 |

| | | | | | | | | | | 272 | | | | | | | |
|----|------------------------|-------------------|-----------------------|-----------------------|-----------------------|----------------------|-------------------|--------------------|-------------------|-------------------|----------------|-------------------|-----------------------|-------------------|------------|-----------------------|---------------------|
| | As | p V | al Le | eu G] 50 | lu G] 00 | u Th | r Hi | в Ту | r Gl 50 | u As 5 | n Gl | y Gli | и Ту | r Il 51 | | e Arg | |
| 5 | CA G1 | A GO | GT GO Ly Al | .u AI | GA GG | G GA y As | C AC p Th | C TT r Ph 52 | e Pn | T AT | C ATO | C AGO | C AA/ C Lys 525 | Gl | A AC | G GTA r Val | 1584 |
| 10 | 110 | 53 | 30 | IT AL | g GI | u As | 53! | r Pro 5 | o Sei | r Glı | ı Asp | 540 | Val | Phe | e Le | T AGA u Arg | 1632 |
| 15 | 549 | 5 | u Gi | у пу | s GI | y As <u>ı</u> 55(| o Tri | o Phe | e G1) | / Glu | 1 Lys 555 | Ala | Leu | Glr | ı Gl | G GAA / Glu 560 | 1680 |
| | GA: As _I | r GT o Va | G AG 1 Ar | A AC. g Th: | A GCA r Ala 569 | a Asr | C GTA | A ATT | GCT Ala | GCA Ala 570 | Glu | GCT Ala | GTA Val | ACC Thr | TG(Cys | C CTT S Leu | 1728 |
| 20 | GTC Val | AT Il | T GA | C AGA P Arg 580 | A WOF | C TCT Ser | TTT Phe | Lys | CAT His 585 | Leu | ATT | GGA Gly | GGG Gly | CTG Leu 590 | Asp | GAT Asp | 1776 |
| 25 | GTI Val | TC' | T AAT r Asi 59! | Luy | A GCA S Ala | TAT Tyr | GAA Glu | GAT Asp 600 | Ala | GAA Glu | GCT Ala | AAA Lys | GCA Ala 605 | AAA Lys | TAT Tyr | GAA Glu | 1824 |
| 30 | GCT Ala | GAZ Glu 610 | | G GCT A Ala | TTC Phe | TTC Phe | GCC Ala 615 | AAC Asn | CTG Leu | AAG Lys | CTG Leu | TCT Ser 620 | GAT Asp | TTC Phe | AAC Asn | ATC Ile | 1872 |
| 35 | 625 | 7.01 | , 1111 | Deu | GGA Gly | 630 | GIY | GIA | Phe | Gly | Arg 635 | Val | Glu | Leu | Val | Gln 640 | 1920 |
| | | _,_ | 001 | GIU | GAA Glu 645 | ser | пуs | Tnr | Phe | Ala 650 | Met | Lys | Ile | Leu | Lys 655 | Lys | 1968 |
| 40 | CGT Arg | CAC | ATT Ile | GTG Val 660 | GAC Asp | ACA Thr | AGA Arg | CAG Gln | CAG Gln 665 | GAG Glu | CAC His | ATC Ile | Arg | TCA Ser 670 | GAG Glu | AAG Lys | 2016 |
| 45 | CAG Gln | ATC Ile | ATG Met 675 | CAG Gln | GGG Gly | GCT Ala | CAT His | TCC Ser 680 | GAT Asp | TTC Phe | ATA Ile | Val . | AGA Arg 685 | CTG Leu | TAC Tyr | AGA Arg | 2064 |
| 50 | ACA Thr | TTT Phe 690 | AAG Lys | GAC Asp | AGC Ser | AAA Lys | TAT Tyr 695 | TTG Leu | TAT Tyr | ATG Met | Leu | ATG (Met (| GAA (| GCT Ala | TGT Cys | CTA Leu | 2112 |
| 55 | GGT Gly 705 | GGA Gly | GAG Glu | CTC Leu | TGG Trp | ACC Thr 710 | ATT Ile | CTC Leu | AGG Arg | Asp . | AGA (Arg (| GGT ? Gly s | TCG ? Ser 1 | TTT | Glu | GAT Asp 720 | 2160 |
| | TCT | ACA | ACC | AGA | TTT | TAC . | ACA (| GCA | TGT (| GTG (| GTA (| GAA (| GCT T | TTT (| GCC | TAT | 2208 27 2 |

| | | | | | | | | | | 273 | | | | | | | |
|----|-----|---------------------|------------|------------|------------|-----|---------------------|------------|------------|------------|-----|------------|------------|------------|------------|------|------|
| | Ser | Thr | Thr | Arg | Phe 725 | Tyr | Thr | Ala | Cys | Val 730 | Val | Glu | Ala | Phe | Ala 735 | Tyr | |
| | CTG | CAT | TCC | AAA | GGA | ATC | ATT | TAC | AGG | GAC | CTC | AAG | CCA | GAA | AAT | CTC | 2256 |
| 5 | Leu | His | Ser | Lys 740 | Gly | Ile | Ile | Tyr | Arg 745 | Asp | Leu | Lys | Pro | Glu 750 | Asn | Leu | |
| | ATC | CTA | GAT | CAC | CGA | GGT | TAT | GCC | AAA | CTG | GTT | GAT | TTT | GGC | TTT | GCA | 2304 |
| 10 | Ile | Leu | Asp 755 | His | Arg | Gly | Tyr | Ala 760 | Lys | Leu | Val | Asp | Phe 765 | Gly | Phe | Ala | |
| | AAG | AAA | ATA | GGA | TTT | GGA | AAG | AAA | ACA | TGG | ACT | TTT | TGT | GGG | ACT | CCA | 2352 |
| 45 | Lys | Lys 7 7 0 | Ile | Gly | Phe | Gly | Lys 7 7 5 | Lys | Thr | Trp | Thr | Phe 780 | Cys | Gly | Thr | Pro | |
| 15 | CAC | m v m | CTIA | aaa | CCN | CNC | 7 TC | N TO C | ama | 220 | *** | GGC | an m | an a | a mm | max. | 2400 |
| | | | | | | | | | | | | Gly | | | | | 2400 |
| | 785 | -7- | • | ,,,,, | 110 | 790 | | 110 | Deu | 71011 | 795 | Oly | | r.op | | 800 | |
| 20 | GCC | GAC | TAC | TGG | TCA | CTG | GGA | ATC | CTA | ATG | TAT | GAA | CTC | CTG | ACT | GGC | 2448 |
| | Ala | Asp | Tyr | Trp | Ser 805 | Leu | Gly | Ile | Leu | Met 810 | Tyr | Glu | Leu | Leu | Thr 815 | Gly | |
| | AGC | CCA | CCT | TTC | TCA | GGC | CCA | GAT | CCT | ATG | AAA | ACC | TAT | AAC | ATC | ATA | 2496 |
| 25 | Ser | Pro | Pro | Phe 820 | Ser | Gly | Pro | Asp | Pro 825 | Met | Lys | Thr | Tyr | Asn 830 | Ile | Ile | |
| | TTG | AGG | GGG | ATT | GAC | ATG | АТА | GAA | TTT | CCA | AAG | AAG | ATT | GCC | AAA | AAT | 2544 |
| 30 | Leu | Arg | Gly 835 | Ilè | Asp | Met | Ile | Glu 840 | Phe | Pro | Lys | Lys | Ile 845 | Ala | Lys | Asn | |
| | GCT | GCT | AAT | TTA | АТТ | AAA | AAA | СТА | TGC | AGG | GAC | AAT | CCA | TCA | GAA | AGA | 2592 |
| | _ | _ | | | | | | | | | | Asn 860 | | | | | |
| 35 | | ~~~ | 3 3 m | mma | | | | - | | ~ | | ~~~ | | ~~~ | | maa | 2540 |
| | | | | | | | | | | | | CAA Gln | | | | | 2640 |
| | 865 | Gly | ASII | Deu | БуБ | 870 | Gly | vai | Буз | Asp | 875 | GIII | nys | 1115 | шуз | 880 | |
| 40 | TTT | GAG | GGC | TTT | AAC | TGG | GAA | GGC | TTA | AGA | AAA | GGT | ACC | TTG | ACA | CCT | 2688 |
| | Phe | Glu | Gly | Phe | Asn 885 | Trp | Glu | Gly | Leu | Arg 890 | Lys | Gly | Thr | Leu | Thr 895 | Pro | |
| | CCT | ATA | ATA | CCA | AGT | GTT | GCA | TCA | CCC | ACA | GAC | ACA | AGT | AAT | TTT | GAC | 2736 |
| 45 | Pro | Ile | Ile | Pro 900 | Ser | Val | Ala | Ser | Pro 905 | Thr | Asp | Thr | Ser | Asn 910 | Phe | Asp | |
| | AGT | TTC | CCT | GAG | GAC | AAC | GAT | GAA | CCA | CCA | CCT | GAT | GAC | AAC | TCA | GGA | 2784 |
| | | | | | | | | | | | | Asp | | | | | |
| 50 | | | 915 | | | | | 920 | | | | | 925 | | | | |
| | | | ATA | | | TAA | | | | | | | | | | | 2802 |
| | Trp | _ | Ile | Asp | Phe | | | | | | | | | | | | |
| 55 | | 930 | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |

274

(2) INFORMATION FOR SEQ ID NO:135:

```
(i) SEQUENCE CHARACTERISTICS:
```

- (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

| 15 | | | | | 5 | | | | | 10 | | | | | 7.5 | Leu |
|----|-----|------|-----|--------|-------|-----|-----|-----|-----|-----|-----|-----|-----|------------|-----|-----------|
| | | | | 20 | | | | | 25 | | | | | 20 | | Gly |
| 20 | | | | | | | | 40 | | | | | 45 | | | lle |
| 20 | | 50 | | | | | 55 | | | | | 60 | | | | Thr |
| | 0.5 | | | | | 70 | | | | | 75 | | | | | Lys 80 |
| 25 | | | | | 85 | | | | | 90 | | | | | 95 | Glu |
| | | | | 100 | | | | | 105 | | | | | 110 | | Glu |
| 20 | | | 110 | | | | | 120 | | | | | 125 | Leu | | Gly |
| 30 | | 130 | | | | | 135 | | | | | 140 | | Leu | | |
| | 143 | | | | | 120 | | | | | 155 | | | Gln | | 160 |
| 35 | | | | | T P P | | | | | 170 | | | | Asp | 175 | |
| | | | | 190 | | | | | 185 | | | | | Gly 190 | | |
| 40 | | | 193 | | | | | 200 | | | | | 205 | Ser | | |
| 40 | | 2.10 | | | | | 215 | | | | | 220 | | Leu | | |
| | | | | | | 230 | | | | | 235 | | | Tyr | | 240 |
| 45 | | | | | 245 | | | | | 250 | | | | Leu | 255 | |
| | | | | 260 | | | | | 265 | | | | | Ala 270 | | |
| 50 | | | 2/5 | | | | | 280 | | | | | 285 | Ile | | |
| 50 | | 290 | | | | | 295 | | | | | 300 | | Pro | | |
| | 303 | | | | | 310 | | | | | 315 | | | Glu | | 220 |
| 55 | | | | | 325 | | | | | 330 | | | | Asp | 225 | |
| | Asp | | SEL | 117.23 | val | inr | гел | Pro | Phe | Tyr | Pro | Lys | Ser | Pro | Gln | Ser |

| | | | | 340 | | | | | 345 | | | | | 350 | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Lys | Asp | Leu 355 | Ile | Lys | Glu | Ala | Ile 360 | Leu | Asp | Asn | Asp | Phe 365 | Met | Lys | Asn |
| 5 | Leu | Glu 370 | Leu | Ser | Gln | Ile | Gln 375 | Glu | Ile | Val | Asp | Cys 380 | Met | Tyr | Pro | Val |
| | Glu 385 | | Gly | Lys | Asp | Ser 390 | Cys | Ile | Ile | Lys | Glu 395 | | Asp | Val | Gly | Ser 400 |
| | | Val | Tyr | Val | | | Asp | Gly | Lys | | | Val | Thr | Lys | | |
| 10 | Val | Lys | Leu | - | 405 Thr | Met | Gly | Pro | - | 410 Lys | Val | Phe | Gly | | 415 Leu | Ala |
| | Ile | Leu | Tyr | 420 Asn | Cys | Thr | Arg | | 425 Ala | Thr | Val | Lys | | 430 Leu | Val | Asn |
| | Val | Lys | 435 Leu | Trp | Ala | Ile | Asp | 440 Arg | Gln | Сув | Phe | Gln | 445 Thr | Ile | Met | Met |
| 15 | Arg | 450 Thr | Gly | Leu | Ile | Lys | 455 His | Thr | Glu | Tyr | Met | 460 Glu | Phe | Leu | Lys | Ser |
| | 465 Val | Pro | Thr | Phe | Gln | 470 Ser | Leu | Pro | Glu | Glu | 475 Ile | Leu | Ser | Lys | Leu | 480 Ala |
| 20 | Asp | Val | Leu | Glu | 485 Glu | Thr | His | Tyr | Glu | 490 Asn | Gly | Glu | Tyr | Ile | 495 Ile | Arg |
| | Gln | Gly | Ala | 500 Arg | Gly | Asp | Thr | Phe | 505 Phe | Ile | Ile | Ser | Lvs | 510 Gly | Thr | Val |
| | | | 515 Thr | | | | | 520 | | | | | 525 | | | |
| 25 | | 530 | Gly | _ | | | 535 | | , · | | _ | 540 | | | | _ |
| | 545 | | Arg | | _ | 550 | _ | | _ | | 555 | | | | | 560 |
| 20 | _ | | _ | | 565 | | | | | 570 | | | | | 575 | |
| 30 | | | Asp | 580 | _ | | | _ | 585 | | | _ | - | 590 | _ | |
| | | | Asn 595 | | | - | | 600 | | | | _ | 605 | _ | _ | |
| 35 | | 610 | Ala | | | | 615 | | | - | | 620 | _ | | | |
| | 11e 625 | Asp | Thr | Leu | Gly | Val 630 | Gly | Gly | Phe | Gly | Arg 635 | Val | Glu | Leu | Val | Gln 640 |
| | Leu | Lys | Ser | Glu | Glu 645 | Ser | Lys | Thr | Phe | Ala 650 | Met | Lys | Ile | Leu | Lys 655 | Lys |
| 40 | _ | | Ile | 660 | | | | | 665 | | | | _ | 670 | | |
| | Gln | Ile | Met 675 | Gln | Gly | Ala | His | Ser 680 | Asp | Phe | Ile | Val | Arg 685 | Leu | Tyr | Arg |
| 45 | Thr | Phe 690 | Lys | Asp | Ser | Lys | Tyr 695 | Leu | Tyr | Met | Leu | Met 700 | Glu | Ala | Cys | Leu |
| | Gly 705 | Gly | Glu | Leu | Trp | Thr 710 | Ile | Leu | Arg | Asp | Arg 715 | Gly | Ser | Phe | Glu | Asp 720 |
| | Ser | Thr | Thr | Arg | Phe 725 | Tyr | Thr | Ala | Суз | Val 730 | Val | Glu | Ala | Phe | Ala 735 | Tyr |
| 50 | Leu | His | Ser | Lys 740 | Gly | Ile | Ile | Tyr | Arg 745 | Asp | Leu | Lys | Pro | Glu 750 | Asn | Leu |
| | Ile | Leu | Asp 755 | His | Arg | Gly | Tyr | Ala 760 | Lys | Leu | Val | Asp | Phe 765 | Gly | Phe | Ala |
| 55 | Lys | Lys 770 | Ile | Gly | Phe | Gly | Lys 775 | Lys | Thr | Trp | Thr | Phe 780 | Сув | Gly | Thr | Pro |
| | Glu | Tyr | Val | Ala | Pro | Glu | Ile | Ile | Leu | Asn | Lys | Gly | His | Asp | Ile | Ser |

| | 270 | | | | | | | | | | | | | | |
|----|--|----|--|--|--|--|--|--|--|--|--|--|--|--|--|
| | 785 790 795 800 | | | | | | | | | | | | | | |
| | Ala Asp Tyr Trp Ser Leu Gly Ile Leu Met Tyr Glu Leu Leu Thr Gly | | | | | | | | | | | | | | |
| 5 | Ser Pro Pro Phe Ser Gly Pro Asp Pro Met Lys Thr Tyr Asn Ile Ile | | | | | | | | | | | | | | |
| | Leu Arg Gly Ile Asp Met Ile Glu Phe Pro Lys Lys Ile Ala Lys Asn | | | | | | | | | | | | | | |
| | Ala Ala Asn Leu Ile Lys Lys Leu Cys Arg Asp Asn Pro Ser Glu Arg 850 855 | | | | | | | | | | | | | | |
| 10 | Leu Gly Asn Leu Lys Asn Gly Val Lys Asp Ile Gln Lys His Lys Trp | | | | | | | | | | | | | | |
| | Phe Glu Gly Phe Asn Trp Glu Gly Leu Arg Lys Gly Thr Leu Thr Pro | | | | | | | | | | | | | | |
| 15 | Pro Ile Ile Pro Ser Val Ala Ser Pro Thr Asp Thr Ser Asn Phe Asp | | | | | | | | | | | | | | |
| | Ser Phe Pro Glu Asp Asn Asp Glu Pro Pro Pro Asp Asp Asn Ser Gly 915 920 925 | | | | | | | | | | | | | | |
| 00 | Trp Asp Ile Asp Phe 930 | | | | | | | | | | | | | | |
| 20 | (2) INFORMATION FOR SEQ ID NO:136: | | | | | | | | | | | | | | |
| | (i) SEQUENCE CHARACTERISTICS: | | | | | | | | | | | | | | |
| 25 | (A) LENGTH: 2799 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear | | | | | | | | | | | | | | |
| | (ii) MOLECULE TYPE: cDNA | | | | | | | | | | | | | | |
| 30 | (ix) FEATURE: | | | | | | | | | | | | | | |
| 35 | (A) NAME/KEY: Coding Sequence(B) LOCATION: 12795(D) OTHER INFORMATION: | | | | | | | | | | | | | | |
| 33 | (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136: | | | | | | | | | | | | | | |
| | ATG GGC ACC TTG CGG GAT TTA CAG TAC GCG CTC CAG GAG AAG ATC GAG | 48 | | | | | | | | | | | | | |
| 40 | Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu 1 5 10 15 | | | | | | | | | | | | | | |
| | GAG CTG AGG CAG CGG GAT GCT CTC ATC GAC GAG CTG GAG CTG GAG TTG | 96 | | | | | | | | | | | | | |
| 45 | Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu 20 25 30 | | | | | | | | | | | | | | |
| | GAT CAG AAG GAC GAA CTG ATC CAG AAG CTG CAG AAC GAG CTG GAC AAG ASD Gln Lys Asp Glu Lou Ilo Cla Lys Asp Glu Lys As | 44 | | | | | | | | | | | | | |
| | Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys 35 40 45 | | | | | | | | | | | | | | |
| 50 | TAC CGC TCG GTG ATC CGA CCA GCC ACC CAG CAG GCG CAG AAG CAG AGC TVr Arg Ser Val Tle Arg Dro Ale The Car Cag CAG GCG CAG AAG CAG AGC | 92 | | | | | | | | | | | | | |
| | Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser 50 60 | | | | | | | | | | | | | | |
| 55 | GCG AGC ACC TTG CAG GGC GAG CCG CGC ACC AAG CGG CAG GCG ATC TCC Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser | 10 | | | | | | | | | | | | | |
| | 65 70 75 80 | | | | | | | | | | | | | | |
| | | _ | | | | | | | | | | | | | |

| | | | | | _ | | | | | GAT Asp 90 | | | | | | | 288 |
|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-------------------|-----|-----|-----|-----|-----|-----|-----|
| 5 . | | | | | | | | | | AAG Lys | | | | | | _ | 336 |
| 10 | እጥሮ | CTT | מאכ | 100 | GAC | արգու | λΤС | አአር | 105 | TTG | CNG | СТС | тСС | 110 | ልጥሮ | CAG | 384 |
| , | | | | | | _ | | | | Leu | _ | | | _ | _ | | 204 |
| 15 | | | | | | | | | | GAG Glu | | | | | | | 432 |
| 20 | | | | | | | | | | CTG Leu | | | | | | | 480 |
| | | | | | | | | | | GTG Val 170 | | | | | | | 528 |
| 25 | | | | | | | | | | ATT Ile | | | | | | | 576 |
| 30 | | | | | | | | | | GTA Val | | | | | | | 624 |
| 35 | | | | | | | | | | AGG Arg | | | | _ | | | 672 |
| 40 | | _ | | | | | | | | GTT Val | | | | | | | 720 |
| | | _ | _ | | | | | | | GAT Asp 250 | | | | | | _ | 768 |
| 45 | | | | | | | | | | CAA Gln | | | | | | | 816 |
| 50 | | | | | | | | | | TAA Asn | | | | | | | 864 |
| 55 | | | | | | | | | | ACT Thr | | | | | | | 912 |

| | | • | | | | | | | | | | | | | | | |
|----|--------------------|-------------------|-----------------------|----------------------|-----------------------|-------------------|--------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-----------------------|------|
| 5 | TT' Pho 30 | C 01 | A GA y Gl | G AA u Ly | A GCO s Ala | TTO Lev 310 | 1 GI1 | G GGC | G GAZ | A GAT 1 Asp | GTC Val | Arg | A ACI | A GC | A AA a As | C GTA n Val 320 | 960 |
| | AT' | r GC e Al | T GC a Al | A GA a Gl | A GCT u Ala 325 | ı vaı | ACC Thi | C TGC | CTI Let | GTC Val | Ile | GA(| C AGA | A GAO | C TC: Se: | r TTT r Phe | 1008 |
| 10 | AA <i>l</i> Lys | A CA s Hi | T TT S Le | G AT u Ile 340 | з сту | GGG Gly | CTC Leu | GAT Asp | GAT Asp 345 |) Val | TCT Ser | 'AA' 'Asr | AAA Lys | GCA Ala 350 | туз | GAA Glu | 1056 |
| 15 | GAT Asp | GC. | A GAZ a Gli 35! | T ATS | r AAA a Lys | GCA Ala | AAA Lys | TAT Tyr 360 | Glu | GCT Ala | GAA Glu | GCG Ala | GCT Ala 365 | Phe | TTC Phe | GCC Ala | 1104 |
| 20 | AAC Asn | Let 370 | л пу: | G CTC | TCT Ser | GAT Asp | TTC .Phe 375 | AAC Asn | ATC Ile | ATT Ile | GAT Asp | ACC Thr 380 | Leu | GGA Gly | GTI Val | GGA Gly | 1152 |
| 25 | GGT Gly 385 | FILE | C GG# ≘ Gly | A CGA / Arg | GTA Val | GAA Glu 390 | CTG Leu | GTC Val | CAG Gln | TTG Leu | AAA Lys 395 | AGT Ser | GAA Glu | GAA Glu | TCC | Lys 400 | 1200 |
| | ACG Thr | TTT Phe | GCA Ala | ATG Met | AAG Lys 405 | ATT Ile | CTC Leu | AAG Lys | AAA Lys | CGT Arg 410 | CAC His | ATT Ile | GTG Val | GAC Asp | ACA Thr 415 | AGA Arg | 1248 |
| 30 | CAG Gln | CAG Gln | GAG Glu | CAC His 420 | ATC Ile | CGC Arg | TCA Ser | GAG Glu | AAG Lys 425 | CAG Gln | ATC Ile | ATG Met | CAG Gln | GGG Gly 430 | GCT Ala | CAT His | 1296 |
| 35 | TCC Ser | GAT Asp | TTC Phe 435 | ATA Ile | GTG Val | AGA Arg | CTG Leu | TAC Tyr 440 | AGA Arg | ACA Thr | TTT Phe | AAG Lys | GAC Asp 445 | AGC Ser | AAA Lys | TAT Tyr | 1344 |
| 40 | TTG Leu | TAT Tyr 450 | ATG Met | TTG Leu | ATG Met | Glu | GCT Ala 455 | TGT Cys | CTA Leu | GGT Gly | GGA Gly | GAG Glu 460 | CTC Leu | TGG Trp | ACC Thr | ATT Ile | 1392 |
| 45 | CTC Leu 465 | AGG Arg | GAT Asp | AGA Arg | GGT Gly | TCG Ser 470 | TTT Phe | GAA Glu | GAT Asp | Ser | ACA Thr 475 | ACC Thr | AGA Arg | TTT Phe | TAC Tyr | ACA Thr 480 | 1440 |
| | GCA Ala | TGT Cys | GTG Val | GTA Val | GAA Glu 485 | GCT Ala | TTT Phe | GCC Ala | TAT Tyr | CTG Leu 490 | CAT His | TCC Ser | AAA Lys | GGA Gly | ATC Ile 495 | ATT Ile | 1488 |
| 50 | TAC Tyr | AGG Arg | GAC Asp | CTC Leu 500 | AAG Lys | CCA (| GAA . Glu . | Asn : | CTC Leu 505 | ATC | CTA (Leu) | GAT Asp | His ! | CGA Arg 510 | GGT Gly | TAT Tyr | 1536 |
| 55 | GCC Ala | AAA Lys | CTG Leu 515 | GTT Val | GAT ' | TTT (| Gly : | TTT (Phe 2 520 | GCA . Ala | AAG Z | AAA : Lys : | Ile | GGA ' Gly 1 525 | TTT Phe | GGA Gly | A AG Lys | 1584 |

279

| | | | | | TGT Cys | | | | | | | 1632 |
|----|---|---|---|---|-------------------|---|---|--|---|--|---|------|
| 5 | | | | | CAT His 550 | | | | | | | 1680 |
| 10 | | | | | CTC Leu | | | | | | | 1728 |
| 15 | | | | | TAT Tyr | _ | _ | | _ | | | 1776 |
| 20 | | | | | ATT Ile | | | | | | | 1824 |
| 25 | | | | | CCA Pro | | | | | | | 1872 |
| | _ | | _ | _ | AAG Lys 630 | | | | | | _ | 1920 |
| 30 | | | | | ACC Thr | | | | | | | 1968 |
| 35 | | | | | AGT Ser | | | | | | | 2016 |
| 40 | | | | | GAC Asp | | | | | | | 2064 |
| 45 | | _ | | | ATG Met | | | | | | | 2112 |
| | | | | | GTC Val 710 | | | | | | | 2160 |
| 50 | | | | | GAG Glu | | | | | | | 2208 |
| 55 | | | | | TGC Cys | | | | | | | 2256 |

280

| 5 | AC(| C CT r Le | C GT u Va 75 | T 111 | C ACC | C CTC | ACC Thi | TAC TY1 760 | G13 | C GTC | G CAG | TGC Cys | TTC Phe 765 | Sei | C CG | C TAC g Tyr | 2304 |
|----|-------------------|-----------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|------|
| | CC(Pro | C GAG O Asj 770 | o ur | C ATO | G AAC | G CAG | CAC His | Asp | TTC Phe | TTC Phe | : AAG : Lys | TCC Ser 780 | Ala | ATC Met | CCC Pro | C GAA o Glu | 2352 |
| 10 | GGC Gly 785 | y | C GTC | C CAC L Glr | G GAG | CGC Arg 790 | Thr | : ATC | TTC | TTC Phe | AAG Lys 795 | Asp | GAC Asp | GGC Gly | AA(Asr | TAC Tyr 800 | 2400 |
| 15 | AAG Lys | ACC Thr | C CGC | GCC Ala | GAG Glu 805 | GTG Val | AAG Lys | TTC Phe | GAG Glu | GGC Gly 810 | GAC Asp | ACC Thr | CTG Leu | GTG Val | AAC Asr 815 | C CGC Arg | 2448 |
| 20 | ATC Ile | GAG Glu | CTC Leu | AAG Lys 820 | GIA | ATC Ile | GAC Asp | TTC Phe | AAG Lys 825 | GAG Glu | GAC Asp | GGC Gly | AAC Asn | ATC Ile 830 | CTG Leu | GGG Gly | 2496 |
| 25 | CAC His | AAG Lys | Leu 835 | GAG Glu | TAC Tyr | AAC Asn | TAC Tyr | AAC Asn 840 | AGC Ser | CAC His | AAC Asn | GTC Val | TAT Tyr 845 | ATC Ile | ATG Met | GCC Ala | 2544 |
| | GAC Asp | AAG Lys 850 | CAG Gln | AAG Lys | AAC Asn | GGC Gly | ATC Ile 855 | AAG Lys | GTG Val | AAC Asn | TTC Phe | AAG Lys 860 | ATC Ile | CGC Arg | CAC His | AAC Asn | 2592 |
| 30 | ATC Ile 865 | GAG Glu | GAC Asp | GGC Gly | AGC Ser | GTG Val 870 | CAG Gln | CTC Leu | GCC Ala | GAC Asp | CAC His 875 | TAC Tyr | CAG Gln | CAG Gln | AAC Asn | ACC Thr 880 | 2640 |
| 35 | CCC Pro | ATC Ile | GGC Gly | GAC Asp | GGC Gly 885 | CCC Pro | GTG Val | CTG Leu | CTG Leu | CCC Pro 890 | GAC Asp | AAC Asn | CAC His | TAC Tyr | CTG Leu 895 | AGC Ser | 2688 |
| 40 | ACC Thr | CAG Gln | TCC Ser | GCC Ala 900 | CTG Leu | AGC Ser | AAA Lys | Asp | CCC Pro 905 | AAC Asn | GAG . Glu | AAG Lys | Arg . | GAT Asp 910 | CAC His | ATG Met | 2736 |
| 45 | GTC Val | CTG Leu | CTG Leu 915 | GAG Glu | TTC Phe | GTG . Val | Inr | GCC Ala 920 | GCC Ala | GGG . Gly | ATC / | Thr | CTC (Leu (925 | GGC Gly | ATG Met | GAC Asp | 2784 |
| | GAG Glu | | | | TAA | | | | | | | | | | | | 2799 |
| 50 | | | (2) | INF | ORMA: | гіои | FOR | SEQ | ID 1 | NO:13 | 37: | | | | | | |

- (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 932 amino acids
 - (B) TYPE: amino acid

55

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser Ala Glu Pro Thr Ala Phe Asp Ile Gln Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser Lys Asp Leu Ile Lys Glu Ala Ile Leu Asp Asn Asp Phe Met Lys Asn Leu Glu Leu Ser Gln Ile Gln Glu Ile Val Asp Cys Met Tyr Pro Val Glu Tyr Gly Lys Asp Ser Cys Ile Ile Lys Glu Gly Asp Val Gly Ser Leu Val Tyr Val Met Glu Asp Gly Lys Val Glu Val Thr Lys Glu Gly Val Lys Leu Cys Thr Met Gly Pro Gly Lys Val Phe Gly Glu Leu Ala Ile Leu Tyr Asn Cys Thr Arg Thr Ala Thr Val Lys Thr Leu Val Asn Val Lys Leu Trp Ala Ile Asp Arg Gln Cys Phe Gln Thr Ile Met Met Arg Thr Gly Leu Ile Lys His Thr Glu Tyr Met Glu Phe Leu Lys Ser Val Pro Thr Phe Gln Ser Leu Pro Glu Glu Ile Leu Ser Lys Leu Ala Asp Val Leu Glu Glu Thr His Tyr Glu Asn Gly Glu Tyr Ile Ile Arg Gln Gly Ala Arg Gly Asp Thr Phe Phe Ile Ile Ser Lys Gly Thr Val Asn Val Thr Arg Glu Asp Ser Pro Ser Glu Asp Pro Val Phe Leu Arg Thr Leu Gly Lys Gly Asp Trp Phe Gly Glu Lys Ala Leu Gln Gly Glu Asp Val Arg Thr Ala Asn Val Ile Ala Ala Glu Ala Val Thr Cys Leu Val Ile Asp Arg Asp Ser Phe Lys His Leu Ile Gly Gly Leu Asp Asp Val Ser Asn Lys Ala Tyr Glu Asp Ala Glu Ala Lys Ala Lys Tyr Glu Ala Glu Ala Ala Phe Phe Ala Asn Leu Lys Leu Ser Asp Phe Asn Ile Ile Asp Thr Leu Gly Val Gly Gly Phe Gly Arg Val Glu Leu Val Gln Leu Lys Ser Glu Glu Ser Lys

| | | | | | | | | | | 282 | 2 | | | | | |
|-----|-----|------------|------------|-------------------|--------------|-------|-------|------------|------------|------------|-------|-------------|-------------|--------------------|-------|--------------|
| | 38 | | | | | 39 | 0 | | | | 39 | 5 | | | | |
| | Th | r Ph | e Al | a Me | t Ly: 40: | s Il | e Le | u Ly | s Ly | s Ar 41 | g Hi | s Il | e Va | l As | | 400 r Arg |
| 5 | Gl | n Gl | n Gl | u Hi 42 | s Ile O | e Ar | g Se | r Gl | u Ly 42 | s Gl | n Il | e Me | t Gl | | | s a His |
| | Se | r As | p Ph 43 | e Ilo | e Val | l Ar | g Le | и Ту 44 | r Ar | g Th | r Ph | e Ly | | | r Ly | s Tyr |
| | Le | и Ту 45 | r Me O | t Le | u Met | : Glu | 1 Ala | а Су | s Le | u Gl | y Gl | y Gl | 44. u Le | s u Tr <u>l</u> |) Th | r Ile |
| 10 | Le: | u Ar 5 | g As | p Arg | g Gly | / Sei | Phe | e Gl | u As | p Se | r Th: | 46 r Th: | r Ar | g Phe | ≘ Ty: | r Thr |
| | | | | | 400 | • | | | | 49 | u Hi: | s Se | | | 40 | 480 e Ile |
| 15 | | | | 200 | , | | | | 50 | u Ile | e Lei | | | C 3 / | | y Tyr |
| | | | | • | | | | 521 | ⊇ Ala | a Ly: | | | E 2 6 | Phe | e Gly | / Lys |
| | | | - | | | | 7.1 | • | | | | - 4 - | . Ala | Pro | | lle |
| 20 | | | | | | 220 | | | | | 555 | | | | | Gly 560 |
| | | | | | 202 | | | | | 570 |) | | | | | Pro |
| 25 | | | | Lys 580 | | | | | 585 | | | | | | | |
| | | | | | | | | 600 | | | | | CAL | | | |
| 30 | | | | Asp | | | O T D | | | | | C 2 A | | | | |
| | | | | Ile | | 030 | | | | | 635 | | | | | - 4 - |
| | | | | Lys | 040 | | | | | 650 | | | | | | |
| 35 | | | | Asp 660 Pro | | | | | 665 | | | | | C70 | | |
| | | | 0,3 | Ala | | | | h H O | | | | | C D E | | | |
| 40 | | | | Ile | | | 030 | | | | | 700 | | | | |
| | | | | Ser | | | | | | | | | | | | |
| 4.5 | | | | Phe | | | | | | | | | | | | |
| 45 | | | Val | 740 Thr | | | | | 745 | | | | | 750 | | |
| | | Asp | | Met | | | | /h() | | | | | 765 | | | |
| 50 | | | | Gln | | | //> | | | | | 700 | | | | |
| | | | | Ala | Glu | ,,, | | | | Gly | 705 | | | | | |
| 55 | | | Leu | Lys (| | | | Phe | Lys | | | | | | | |
| | | | | Glu ' | | | | | H25 | | | | | 000 | | |
| | | | | | | | | | | | | | | | | |

| • | | | 835 | | | | | 840 | | | | | 845 | | | _ | |
|----------------|------------|------------|------------|------------|------------|------------|------------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|----------|
| | Asp | Lys 850 | Gln | Lys | Asn | Gly | Ile 855 | Lys | Val | Asn | Phe | 860 Lys | Ile | Arg | His | Asn | |
| 5 | Ile 865 | Glu | Asp | Gly | Ser | Val 870 | Gln | Leu | Ala | Asp | His 875 | Tyr | Gln | Gln | Asn | Thr 880 | |
| | | Ile | Gly | Asp | Gly 885 | Pro | Val | Leu | Leu | Pro 890 | Asp | Asn | His | Tyr | Leu 895 | Ser | |
| | Thr | Gln | Ser | Ala 900 | | Ser | Lys | Asp | Pro 905 | | Glu | Lys | Arg | Asp 910 | _ | Met | |
| 10 | Val | Leu | Leu 915 | | Phe | Val | Thr | | | Gly | Ile | Thr | Leu 925 | | Met | Asp | |
| | Glu | Leu 930 | | Lys | | | | 920 | | | | | 923 | | | | |
| 15 | | 230 | (2) | . TXT | ZODM7 | יייי איי | T FO | , er. | מד ה | NO. T | 20. | | | | | | |
| 13 | | | | | | ATION | | | | NO: | .36; | | | | | | |
| | | (: | | _ | | 2184 | | | | | | | | | | | |
| 20 | | | | | | ones: | | | = | | | | | | | | |
| | | | (D) | TOPO | DLOG | Y: 1: | inear | • | | | | | | | | | |
| | | • | | OLEC | | TYP | E: cI | ANC | | | | | | | | | |
| 25 | | · | | | | EY: (| rodit | na 54 | miei | nce | | | | | | | |
| | | | (B) | LO | CATIO | ON: 3 | ι2 | 2181 | -que. | | | | | | | | |
| | | | | | | INFO | | | | | | | | | | | |
| 30 | | () | (1) : | SEQUI | ENCE | DESC | CRIP. | NOL | : SE(| מז כ | NO: | 138: | | | | | |
| | | | | | | GAG Glu | | | | | | | | | | | 48 |
| 35 | 1 | | | - | 5 | | | | | 10 | | | | | 15 | | |
| | | | | | | GAC Asp | | | | | | | | | | | 96 |
| | Val | Giu | ьец | 20 20 | Gry | АБР | vai | ASII | 25 25 | HIS | Буз | FIIC | | 30 | DCI | Gry | |
| 40 | | | | | | GCC | | | | | | | | | | | 144 |
| | Glu | GIY | 35 | GIY | Asp | Ala | Thr | 1yr 40 | Gly | гÀг | Leu | Thr | 16u 45 | гÀг | Pne | 11e | |
| | | | | | | CTG | | | | | | | | | | | 192 |
| 45 | Cys | Thr 50 | Thr | Gly | rys | Leu | Pro 55 | Val | Pro | Trp | Pro | Thr 60 | Leu | Val | Thr | Thr | |
| | CTG | ACC | TAC | GGC | GTG | CAG | TGC | TTC | AGC | CGC | TAC | ccc | GAC | CAC | ATG | AAG | 240 |
| າ 50 | Leu 65 | Thr | Tyr | Gly | Val | Gln 70 | Cys | Phe | Ser | _ | Tyr 75 | Pro | Asp | His | Met | Lys 80 | |
| | | CAC | GAC | דידיכי | ጥጥር | AAG | דככ | GCC | ልፕር | CCC | GAA | GGC | TAC | GTC | CAG | GAG | 288 |
| | | | | | | Lys | | | | | | | | | | _ | |
| 55 | | | | mer e | | | | | | | m= - | | | | | a » c | 226 |
| | CGC | ACC | ATC | TTC | TTC | AAG | GAC | GAC | GGC | AAC | TAC | AAG | ACC | CGC | GCC | GAG | 336 2 |

| | | | | | | | | | | 284 | | | | | | | |
|----|-------------------|-------------------|--------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|------|
| | Ar | g T | hr I | le Ph 10 | ne Ph | ie Ly | aA e | p As | p Gl 10 | y As 5 | п Ту | r Ly | s Th | r Ar 11 | | a Glu | |
| 5 | | | 1: | 15 | u Gi | умъ | b m | 12 | u Va O | 1 As: | n Ar | g Ile | e Gl: 129 | ı Le | и Ьу | s Gly | 384 |
| 10 | | 13 | 00 | те Бу | 5 61 | u AS | 13! | y Ası 5 | n II | e Lei | u Gl | y His 140 | Lys | Le | u Gl | G TAC u Tyr | 432 |
| 15 | 145 | 5 | | | - 111 | 150 | o va. | т тут | c 116 | e Met | 15: | a Asp 5 | Lys | Glı | 1 Ьу | G AAC s Asn 160 | 480 |
| | 7 | | c by | o va | 16 | 5 | : rAs | 3 11e | Arg | 7 His 170 | Ası | ı Ile | Glu | . Asp | 17: | | 528 |
| 20 | GTG Val | G CA | G CT n Le | C GCG u Ala 180 | , vol | C CAC His | TAC Tyr | CAG Gln | CAC Gln 185 | l Asn | ACC Thr | CCC Pro | ATC Ile | GGC Gly 190 | Ası | G GGC | 576 |
| 25 | CCC Pro | Va. | G CTO Let 19 | 4 100 | CCC Pro | GAC Asp | AAC Asn | CAC His 200 | TAC | CTG Leu | AGC Ser | ACC Thr | CAG Gln 205 | TCC | GCC | CTG Leu | 624 |
| 30 | AGC Ser | AA Lys 210 | | CCC Pro | AAC Asn | GAG Glu | AAG Lys 215 | CGC Arg | GAT Asp | CAC His | ATG Met | GTC Val 220 | CTG Leu | CTG Leu | GAG Glu | TTC | 672 |
| 35 | 225 | | | | GLY | 230 | inr | ьец | GIY | Met | Asp 235 | GAG Glu | Leu | Tyr | Lys | Ser 240 | 720 |
| | GGA Gly | CTC | AGA Arg | TCT Ser | CGA Arg 245 | GGC Gly | ACC Thr | ATG Met | AGC Ser | GAC Asp 250 | GTG Val | GCT Ala | ATT Ile | GTG Val | AAG Lys 255 | GAG Glu | 768 |
| 40 | GGT Gly | TGG Trp | CTG Leu | CAC His 260 | AAA Lys | CGA Arg | GGG Gly | GAG Glu | TAC Tyr 265 | ATC Ile | AAG Lys | ACC Thr | Trp | CGG Arg 270 | CCA Pro | CGC Arg | 816 |
| 45 | TAC Tyr | TTC Phe | CTC Leu 275 | CTC Leu | AAG Lys | AAT Asn | GAT Asp | GGC Gly 280 | ACC Thr | TTC Phe | ATT Ile | Gly | TAC Tyr 285 | AAG Lys | GAG Glu | CGG Arg | 864 |
| 50 | | CAG Gln 290 | GAT Asp | GTG Val | GAC Asp | CAA Gln | CGT Arg 295 | GAG Glu | GCT Ala | CCC Pro | CTC Leu | AAC Asn 300 | AAC Asn | TTC Phe | TCT Ser | GTG Val | 912 |
| 55 | GCG Ala 305 | CAG Gln | TGC Cys | CAG Gln | CTG Leu | ATG Met 310 | AAG : | ACG (| GAG Glu | Arg : | CCC Pro 315 | CGG (Arg 1 | CCC / Pro / | AAC Asn | ACC Thr | TTC Phe 320 | 960 |
| | ATC I | ATC | CGC | TGC | CTG | CAG ' | TGG 1 | ACC 2 | ACT (| GTC 1 | ATC | GAA (| CGC A | ACC ' | TTC | CAT | 1008 |

| | | | | | | | | | | 285 | | | | | | | |
|----|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------------|------------|------|
| | Ile | Ile | Arg | Cys | Leu 325 | Gln | Trp | Thr | Thr | Val 330 | Ile | Glu | Arg | Thr | Phe 335 | His | |
| 5 | | | | | GAG Glu | | | | | | | | | | | | 1056 |
| 10 | | | | | CTC Leu | | | | | | | | | | | | 1104 |
| 15 | | | | | AGT Ser | | | | | | | | | _ | _ | | 1152 |
| 10 | | | | | AAG Lys | | | | | | | | | | | | 1200 |
| 20 | | | | | AAG Lys 405 | | | | | | | - | | _ | | | 1248 |
| 25 | | | | | CGC Arg | | | | | | | | | | _ | | 1296 |
| 30 | | | | | GAC Asp | | | | | | | | | | | | 1344 |
| | | | | | AGG Arg | | | | | | | | | | | | 1392 |
| 35 | | | | | CGC Arg | | | | | | | | | | | | 1440 |
| 40 | | | | | CAC His 485 | | | | | | | | | _ | | CGG Arg | 1488 |
| 45 | | | | | GGC Gly | | | | | | | | | | | _ | 1536 |
| 50 | | | | | GTG Val | | | | | | | | | | | | 1584 |
| | | | | | GGG Gly | | | | | | | | | | | AAG Lys | 1632 |
| 55 | GAG | GGG | ATC | AAG | GAC | GGT | GCC | ACC | ATG | AAG | ACC | TTT | TGC | GGC | ACA | CCT | 1680 |

286

| | | | | | | | | | | 200 | | | | | | | |
|----|-------------------|------------|-------------------|----------------------|---------------------|-------------------|-----------------|--------------|-------------------|-------------------|-------------------|------------|------------|-------------------|-------------------|-------------------|------|
| | Glu 545 | Gly | Ile | Lys | Asp | Gly 550 | Ala | Thr | Met | Lys | Thr 555 | | Сув | Gly | Thr | Pro 560 | |
| 5 | GAG Glu | TAC Tyr | CTG | GCC | Pro | Glu | GTG Val | CTG Leu | GAG Glu | GAC Asp 570 | AAT Asn | GAC Asp | TAC Tyr | GGC Gly | CGT Arg 575 | GCA Ala | 1728 |
| 10 | val | Asp | Trp | Trp 580 | Gly | Leu | Gly | Val | 585 | Met | Tyr | Glu | Met | Met 590 | Cys | Gly | 1776 |
| 15 | Arg | Leu | Pro 595 | Phe | Tyr | Asn | Gln | Asp 600 | | Glu | Lys | Leu | Phe 605 | Glu | Leu | Ile | 1824 |
| | Leu | мес 610 | GIu | Glu | Ile | Arg | Phe 615 | Pro | CGC Arg | Thr | Leu | Gly 620 | Pro | Glu | Ala | Lys | 1872 |
| 20 | TCC Ser 625 | TTG Leu | CTT Leu | TCA Ser | GGG Gly | CTG Leu 630 | CTC Leu | AAG Lys | AAG Lys | GAC Asp | CCC Pro 635 | AAG Lys | CAG Gln | AGG Arg | CTT Leu | GGC Gly 640 | 1920 |
| 25 | GGG Gly | GGC Gly | TCC Ser | GAG Glu | GAC Asp 645 | GCC Ala | AAG Lys | GAG Glu | ATC Ile | ATG Met 650 | CAG Gln | CAT His | CGC Arg | TTC Phe | TTT Phe 655 | GCC Ala | 1968 |
| 30 | GGT Gly | ATC Ile | GTG Val | TGG Trp 660 | CAG Gln | CAC His | GTG Val | TAC Tyr | GAG Glu 665 | AAG Lys | AAG Lys | CTC Leu | AGC Ser | CCA Pro 670 | CCC Pro | TTC Phe | 2016 |
| 35 | rys | Pro | 675 | Val | Thr | Ser | Glu | Thr 680 | GAC Asp | Thr | Arg | Tyr | Phe 685 | Asp | Glu | Glu | 2064 |
| | Pne | 690 | Ala | Gln | Met | Ile | Thr 695 | Ile | ACA Thr | Pro | Pro | Asp 700 | Gln | Asp | Asp | Ser | 2112 |
| 40 | ATG Met 705 | GAG Glu | TGT Cys | GTG Val | GAC Asp | AGC Ser 710 | GAG Glu | CGC Arg | AGG Arg | CCC Pro | CAC His 715 | TTC Phe | CCC Pro | CAG Gln | TTC Phe | TCC Ser 720 | 2160 |
| 45 | | TCG Ser | | Ser | | | | TGA | | | | | | | | | 2184 |
| 50 | | (i | (2)) SE | | | | | | ID : | NO:1 | 39: | | | | | | |
| 55 | | | (A) (B) (C) | LENG TYPE STRA | TH: : am NDED | 727 . ino : | aminacid cid | o ac ngle | ids | | | | | | | | |
| | | | | | | | | | | | | | | | | | |

287

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

| 5 | | `` | , | J_Q01 | 21.02 | | | 1011 | . 52, | , 10 | 110. | | | | | |
|----|----------|-----|-----|-------|------------|-----|-----|------|-------|-----------|------|-----|-----|-----|-----------|-----|
| | Met 1 | Val | Ser | Lys | Gly 5 | Glu | Glu | Leu | Phe | Thr 10 | Gly | Val | Val | Pro | Ile 15 | Leu |
| | | | | 20 | Gly | | | | 25 | | | | | 30 | | |
| 10 | | _ | 35 | _ | Asp | | | 40 | _ | - | | | 45 | _ | | |
| | _ | 50 | | - | Lys | | 55 | | | - | | 60 | | | | |
| 15 | 65 | | | | Val | 70 | - | | | _ | 75 | | _ | | | 80 |
| | | | | | Phe 85 | | | | | 90 | | | _ | | 95 | |
| • | | | | 100 | Phe | | | | 105 | | | | | 110 | | |
| 20 | | _ | 115 | | Gly | = | | 120 | | | _ | | 125 | | - | • |
| | | 130 | | | Glu | | 135 | | | | - | 140 | - | | | |
| 25 | 145 | | | | His | 150 | | _ | | | 155 | - | - | | • | 160 |
| | | | | | Asn 165 | | | | | 170 | | | | | 175 | |
| 30 | | | | 180 | Asp | | | | 185 | | | | | 190 | | |
| 30 | | | 195 | | Pro | _ | | 200 | - | | | | 205 | | | |
| | | 210 | _ | | Asn | | 215 | _ | _ | | | 220 | | | | |
| 35 | 225 | | | | Gly Arg | 230 | | | | | 235 | | | | | 240 |
| | | | \ | | 245 Lys | - | | | | 250 | | | | | 255 | |
| 40 | | | | 260 | Lys | | | | 265 | | _ | | _ | 270 | | |
| 40 | | | 275 | | Asp | | | 280 | | | | _ | 285 | _ | | _ |
| | | 290 | _ | | Leu | | 295 | | | | | 300 | | | | |
| 45 | 305 | | | | Leu | 310 | | | | | 315 | | | | | 320 |
| | | | _ | _ | 325 Glu | | _ | | | 330 | | | _ | | 335 | |
| 50 | | | | 340 | Leu | | _ | | 345 | _ | | | | 350 | | |
| | | | 355 | | Ser | | | 360 | | | | | 365 | | | |
| | | 370 | | | Lys | | 375 | | | | | 380 | | | | |
| 55 | 385 | | | | Lys | 390 | | | | | 395 | | | | _ | 400 |
| | - | | | - | • | - 4 | | | - 1 | - | _ | _ | | | 4 - | |

288

| | _ | | | | 405 | | | | | 410 | | | | | 415 | |
|----|------------|------------|------------|--------------|------------|--------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | | | | 420 | | | | | 425 | | | | | 430 | | Val |
| 5 | | | 435 | | | | | 440 | | | | | 445 | | | Val |
| | Leu | Gln 450 | Asn | Ser | Arg | His | Pro 455 | | Leu | Thr | Ala | Leu 460 | Lys | Tyr | Ser | Phe |
| | Gln 465 | Thr | His | Asp | Arg | Leu 470 | Cys | | Val | Met | Glu 475 | Tyr | Ala | Asn | Gly | Gly |
| 10 | Glu | Leu | Phe | Phe | His 485 | | | Arg | Glu | Arg | Val | Phe | Ser | Glu | | 480 Arg |
| | Ala | Arg | Phe | Tyr 500 | Gly | Ala | Glu | Ile | Val 505 | Ser | Ala | Leu | Asp | | 495 Leu | His |
| 15 | Ser | Glu | Lys 515 | Asn | | Val | Tyr | Arg 520 | | | Lys | Leu | | 510 Asn | Leu | Met |
| | Leu | Asp 530 | | Asp | Gly | His | Ile 535 | | Ile | Thr | Asp | Phe 540 | 525 Gly | Leu | Cys | Lys |
| | Glu 545 | Gly | Ile | Lys | Asp | Gly 550 | Ala | Thr | Met | Lys | Thr 555 | Phe | Cys | Gly | Thr | |
| 20 | Glu | Tyr | Leu | Ala | Pro 565 | | | Leu | Glu | Asp 570 | Asn | Asp | Tyr | Gly | Arg 575 | 560 Ala |
| | Val | Asp | Trp | Trp 580 | Gly | Leu | Gly | Val | Val 585 | | Tyr | Glu | Met | Met 590 | Cys | Gly |
| 25 | Arg | Leu | Pro 595 | Phe | Tyr | Asn | Gln | Asp 600 | His | Glu | Lys | Leu | Phe 605 | Glu | Leu | Ile |
| | Leu | Met 610 | Glu | Glu | Ile | Arg | Phe 615 | | Arg | Thr | Leu | Gly 620 | Pro | Glu | Ala | Lys |
| | Ser 625 | Leu | Leu | Ser | Gly | Leu 630 | Leu | Lys | Lys | Asp | Pro 635 | Lys | Gln | Arg | Leu | Gly 640 |
| 30 | Gly | Gly | Ser | Glu | Asp 645 | Ala | Lys | Glu | Ile | Met 650 | Gln | His | Arg | Phe | Phe 655 | Ala |
| | Gly | Ile | Val | Trp 660 | Gln | His | Val | Tyr | Glu 665 | Lys | Lys | Leu | Ser | Pro 670 | Pro | Phe |
| 35 | Lys | Pro | Gln 675 | Val | Thr | Ser | Glu | Thr 680 | Asp | Thr | Arg | Tyr | Phe 685 | Asp | Glu | Glu |
| | | 690 | | Gln | | | 695 | | | | | 700 | Gln | | | |
| | 705 | | | Val | | 710 | | Arg | Arg | Pro | His 715 | Phe | Pro | Gln | Phe | Ser 720 |
| 40 | Tyr | Ser | Ala | Ser | Ser 725 | Thr | Ala | | | | | | | | | |
| | | | (2) | INF | ORMA | TION | FOR | SEC | ID | NO:1 | 40: | | | | | |
| 45 | | | | | | | | | | | | | | | | |
| 40 | | (1 |) SE | QUEN | CE C | HARA | CTER | ISTI | CS: | | | | | | | |
| | | | (B) | LENG TYPE | : nu | 2394 Clei | e bas | e pa | ırs | | | | | | | |
| | | | (C) | STRA | NDED | NESS | : si | nale | | | | | | | | |
| | | | (D) | торо | LOGY | : li | near | 3 | | | | | | | | |
| 50 | | , . | | | | | | | | | | | | | | |
| | | | | OLEC EATU | | TYPE | : cD | NA | | | | | | | | |
| | | | (A) | NAM | E/KE | Y: C | odin | g Se | auen | ce | | | | | | |
| 55 | | | (B) | LOC | ATIO: | N: 1 | 2 | 391 | . | | | | | | | |

(D) OTHER INFORMATION:

289

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

| 5 | | GAC Asp | | | | | | | | | | | | | | | 48 |
|----|------------|------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|----------|
| 10 | | GGC Gly | | | | | | | | | | | | | | | 96 |
| 15 | | TTC Phe | | | | | | | | | | | | | | | 144 |
| | | AGG Arg 50 | | | | | | | | | | | | | | | 192 |
| 20 | | TAC Tyr | | | | | | | | | | | | | | | 240 |
| 25 | | CCT Pro | | | | | | | | | | | | | | | 288 |
| 30 | | GGC Gly | | | | | | | | | | | | | | | 336 |
| 35 | Phe | CAG Gln | Asn 115 | Leu | Gly | Ile | Gln | Cys 120 | Val | Lys | Lys | Arg | Asp 125 | Leu | Glu | Gln | 384 |
| | Ala | Ile 130 | Ser | Gln | Arg | Ile | Gln 135 | Thr | Asn | Asn | Asn | Pro 140 | Phe | Gln | Val | Pro | 432 |
| 40 | Ile 145 | GAA Glu | Glu | Gln | Arg | Gly 150 | Asp | Tyr | Asp | Leu | Asn 155 | Ala | Val | Arg | Leu | Сув 160 | 480 |
| 45 | Phe | CAG Gln | Val | Thr | Val 165 | Arg | Asp | Pro | Ser | Gly 170 | Arg | Pro | Leu | Arg | Leu 175 | Pro | 528 |
| 50 | Pro | GTC Val | Leu | Pro 180 | His | Pro | Ile | Phe | Asp 185 | Asn | Arg | Ala | Pro | Asn 190 | Thr | Ala | 576 |
| 55 | Glu | CTC | Lys 195 | Ile | Cys | Arg | Val | Asn 200 | Arg | Asn | Ser | Gly | Ser 205 | Cys | Leu | Gly | 624 |
| | GGG | GAT | GAG | AIC | 110 | CIA | CTG | TGT | GAC | AAG | GIG | CAG | AAA | GAG | GAC | AII | 672 2 |

| | | | | | | | | | | 290 | | | | | | | |
|----|-------------------|-------------------|----------------------------|-------------------|-----------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-----------------------|-------------------|
| | Gly | / As 21 | p Gl 0 | u Il | e Ph | e Lei | 1 Let 21! | и Су: 5 | s Asp | Lys | s Val | 1 Glr 220 | | s Glı | ı Ası | p Ile | |
| 5 | GA0 Glu 225 | ı va | G TA | T TT | C ACC | G GG# c Gly 230 | Pro | A GGG | C TGC Y Trp | GAC Glu | G GC0 1 Ala 235 | a Arg | GGC Gly | TCC Ser | TT' | T TCG E Ser 240 | 720 |
| 10 | CA# Gln | A GC | T GA' a As _l | r GTO P Val | G CAC l His 245 | 3 Arg | CAA Glr | A GTO | G GCC L Ala | : ATT | : Val | TTC Phe | CGG | ACC Thr | CCT Pro 255 | CCC Pro | 768 |
| 15 | ТАС Туг | GC | A GA(a Asp | 260 260 | Ser | CTG Leu | Gln | GCT Ala | CCT Pro 265 | Val | CGT Arg | GTC Val | TCC | Met 270 | Glr | CTG Leu | 816 |
| | CGG Arg | CG(| G CCT g Pro 275 | Ser | GAC Asp | CGG Arg | GAG Glu | Leu 280 | Ser | GAG Glu | CCC Pro | ATG Met | GAA Glu 285 | TTC Phe | CAG Gln | TAC Tyr | 864 |
| 20 | CTG Leu | Pro 290 | Asp | ACA Thr | GAC Asp | GAT Asp | CGT Arg 295 | His | CGG Arg | ATT Ile | GAG Glu | GAG Glu 300 | AAA Lys | CGT Arg | AAA Lys | AGG Arg | 912 |
| 25 | ACA Thr 305 | TAT | GAG | ACC Thr | TTC Phe | AAG Lys 310 | AGC Ser | ATC Ile | ATG Met | AAG Lys | AAG Lys 315 | AGT Ser | CCT Pro | TTC Phe | AGC Ser | GGA Gly 320 | 960 |
| 30 | CCC Pro | ACC | GAC Asp | CCC Pro | CGG Arg 325 | CCT Pro | CCA Pro | CCT Pro | CGA Arg | CGC Arg 330 | ATT Ile | GCT Ala | GTG Val | CCT Pro | TCC Ser 335 | CGC Arg | 1008 |
| 35 | AGC Ser | TCA Ser | GCT Ala | TCT Ser 340 | GTC Val | CCC Pro | AAG Lys | CCA Pro | GCA Ala 345 | CCC Pro | CAG Gln | CCC Pro | TAT Tyr | CCC Pro 350 | TTT Phe | ACG Thr | 1056 |
| | TCA Ser | TCC Ser | CTG Leu 355 | AGC Ser | ACC Thr | ATC Ile | AAC Asn | TAT Tyr 360 | GAT Asp | GAG Glu | TTT Phe | CCC Pro | ACC Thr 365 | ATG Met | GTG Val | TTT Phe | 1104 |
| 40 | CCT Pro | TCT Ser 370 | GGG Gly | CAG Gln | ATC Ile | AGC Ser | CAG Gln 375 | GCC Ala | TCG Ser | GCC Ala | TTG Leu | GCC Ala 380 | CCG Pro | GCC Ala | CCT Pro | CCC Pro | 1152 |
| 45 | CAA Gln 385 | GTC Val | CTG Leu | CCC Pro | CAG Gln | GCT Ala 390 | CCA Pro | GCC Ala | CCT Pro | GCC Ala | CCT Pro 395 | GCT Ala | CCA Pro | GCC Ala | ATG Met | GTA Val 400 | 1200 |
| 50 | TCA Ser | GCT Ala | CTG Leu | GCC Ala | CAG Gln 405 | GCC Ala | CCA Pro | GCC Ala | CCT Pro | GTC Val 410 | CCA Pro | GTC Val | CTA Leu | GCC Ala | CCA Pro 415 | GGC Gly | 1248 |
| 55 | CCT Pro | CCT Pro | CAG Gln | GCT Ala 420 | GTG Val | GCC Ala | CCA Pro | CCT Pro | GCC Ala 425 | CCC Pro | AAG Lys | CCC . Pro ' | Thr | CAG Gln 430 | GCT Ala | GGG Gly | 1296 |
| | GAA | GGA | ACG | CTG | TCA | GAG | GCC | CTG | CTG | CAG | CTG | CAG ' | rtt (| GAT | GAT | GAA | 1344 29 |

| | | | | | | | | | | 291 | | | | | | | |
|----|-----|-----|------------|-----|-------------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|------|
| | Glu | Gly | Thr 435 | Leu | Ser | Glu | Ala | Leu 440 | Leu | Gln | Leu | Gln | Phe 445 | Asp | Asp | Glu | |
| 5 | | | | | TTG Leu | | | | | | | | | | | | 1392 |
| 10 | | | | | GTC Val | | | | | | | | | | | | 1440 |
| 15 | | | | | GCC Ala 485 | | | | | | | | | | | | 1488 |
| | | | | | ACT Thr | | | | | | | | | | | | 1536 |
| 20 | | | | | CCA Pro | | | | | | | | | | | | 1584 |
| 25 | | | | | GAC Asp | | | | | | | | | | | | 1632 |
| 30 | | | | | ATC Ile | | | | | | | | | | | _ | 1680 |
| 35 | | | | | GAG Glu 565 | | | | | | | | | | | _ | 1728 |
| 33 | | | | | GTA Val | | | | | | | | | | | _ | 1776 |
| 40 | | | | | ACC Thr | | | | | | | | | | | | 1824 |
| 45 | | | | | CCC Pro | | | | | | | | | | | | 1872 |
| 50 | | | | | TGC Cys | | | | | | | | | | | | 1920 |
| 55 | | | | | TCC Ser 645 | | | | | | | | | | | | 1968 |
| 55 | ATC | TTC | TTC | AAG | GAC | GAC | GGC | AAC | TAC | AAG | ACC | CGC | GCC | GAG | GTG | AAG | 2016 |

| | | | | | | | | | | 292 | | | | | | | |
|----|-------------------|-------------------|---------------------------|------------------------------|---------------------|------------------------|------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------|------|
| | Ile | Phe | Phe | 660 | Asp | Asp | Gly | Asr | Tyr 665 | | Thr | Arg | Ala | Glu 670 | | Lys | |
| 5 | TTC Phe | GAG Glu | GGC Gly 675 | Asp | ACC | CTG Leu | GTG Val | AAC Asn 680 | Arg | ATC Ile | GAG Glu | CTG Leu | AAG Lys 685 | GGC Gly | ATC | GAC Asp | 2064 |
| 10 | TTC Phe | Lys 690 | GIu | GAC Asp | GGC Gly | AAC Asn | ATC Ile 695 | CTG Leu | GGG Gly | CAC His | AAG Lys | CTG Leu 700 | GAG Glu | TAC Tyr | AAC Asn | TAC Tyr | 2112 |
| 15 | 705 | Ser | His | Asn | Val | TAT Tyr 710 | Ile | Met | Ala | Asp | Lys 715 | Gln | Lys | Asn | Gly | Ile 720 | 2160 |
| | AAG Lys | GTG Val | AAC Asn | TTC Phe | AAG Lys 725 | ATC Ile | CGC Arg | CAC His | AAC Asn | ATC Ile 730 | GAG Glu | GAC Asp | GGC Gly | AGC Ser | GTG Val 735 | CAG Gln | 2208 |
| 20 | CTC Leu | GCC Ala | GAC Asp | CAC His 740 | TAC Tyr | CAG Gln | CAG Gln | AAC Asn | ACC Thr 745 | CCC Pro | ATC Ile | GGC Gly | GAC Asp | GGC Gly 750 | CCC Pro | GTG Val | 2256 |
| 25 | CTG Leu | CTG Leu | CCC Pro 755 | GAC Asp | AAC Asn | CAC His | TAC Tyr | CTG Leu 760 | AGC Ser | ACC Thr | CAG Gln | TCC Ser | GCC Ala 765 | CTG Leu | AGC Ser | AAA Lys | 2304 |
| 30 | GAC Asp | CCC Pro 770 | AAC Asn | GAG Glu | AAG Lys | CGC Arg | GAT Asp 775 | CAC His | ATG Met | GTC Val | CTG Leu | CTG Leu 780 | GAG Glu | TTC Phe | GTG Val | ACC Thr | 2352 |
| 35 | GCC Ala 785 | GCC Ala | GGG Gly | ATC Ile | ACT Thr | CTC Leu 790 | GGC Gly | ATG Met | GAC Asp | GAG Glu | CTG Leu 795 | TAC Tyr | AAG Lys | TAA | | | 2394 |
| | | | (2) | TNE | ODMA | TTON | EOD | ana | | | | | | | | | |
| 40 | | (i |) SE (A) (B) (C) | QUEN LENG TYPE STRA | CE C TH: : am | HARA 797 ino NESS : li | CTER amin acid : si | ISTI o ac | CS: | NO:1 | 41: | | | | | | |
| 45 | | (v |) FR | AGME | NT T | TYPE YPE: | int | erna | .1 | | | | | | | | |
| | | (x | i) s | EQUE | NCE : | DESCI | RIPT | ION: | SEQ | ID I | NO:1 | 41: | | | | | |
| 50 | Met . 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| | Ser | | - | 2 U | | | | | 25 | | | | - | a n | | | |
| 55 | Arg | | 33 | | | | 4 | 10 | | | | | 15 | | | | |
| | Glu Z | ura : | SET . | TITE A | sp : | inr 7 | hr I | ъys | Thr 1 | His 1 | Pro ? | Thr : | Ile I | ys : | Ile i | Asn | |

| | | 50 | | | | | 55 | | | | | 60 | | | | |
|----|-------|------------|----------|-------------|-----------|----------|-------------|------|-------|-----|------------|------------|------|-----------|----------|-----------------|
| | Gly | Tyr | Thr | Gly | Pro | Gly | Thr | Val | Arg | Ile | Ser | Leu | Val | Thr | Lys | Asp |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| | Pro | Pro | His | Arg | Pro | His | Pro | His | Glu | Leu | Val | Gly | Lys | Asp | Cys | Arg |
| 5 | | | | | 85 | | | | | 90 | | | | | 95 | |
| | Asp | Gly | Phe | - | Glu | Ala | Glu | Leu | | Pro | Asp | Arg | Cys | | His | Ser |
| | | | | 100 | | | | _ | 105 | _ | _ | | _ | 110 | | |
| | Phe | Gln | | Leu | GIA | He | GIn | | Val | Lys | Lys | Arg | | Leu | Glu | Gin |
| 40 | | ~ 3 | 115 | ~1 . | | - 7 - | G 1. | 120 | | | _ | | 125 | ~1 | | 5 |
| 10 | Ala | | ser | GIN | Arg | TTE | | Thr | Asn | Asn | Asn | Pro | Pne | Gin | vaı | Pro |
| | Tlo | 130 | C111 | Gln | 7 ~~ | Clv | 135 | Т175 | 7 ~~ | Lou | 700 | 140 | 17-1 | 7 ~~ | Lou | Cara |
| | 145 | GIU | Giu | GIII | Arg | 150 | Asp | ıyı | Авр | ьец | 155 | Ala | vai | Arg | ьец | 160 |
| | | Gln | Val | Thr | Val | | Aen | Dro | Cer | Gly | | Pro | Len | Ara | I.eu | |
| 15 | FIIC | Gin | Val | 1111 | 165 | AL 9 | мэр | FIU | JUL | 170 | Ar 9 | FIO | БСи | n. y | 175 | 110 |
| 10 | Pro | Val | Leu | Pro | | Pro | Tle | Phe | Asp | | Ara | Ala | Pro | Asn | | Ala |
| | | | | 180 | | | | | 185 | | | | | 190 | | |
| | Glu | Leu | Lys | | Cys | Arq | Val | Asn | | Asn | Ser | Gly | Ser | | Leu | Gly |
| | | | 195 | | • | _ | | 200 | , | | | • | 205 | • | | • |
| 20 | Gly | Asp | Glu | Ile | Phe | Leu | Leu | Cys | Asp | Lys | Val | Gln | Lys | Glu | Asp | Ile |
| | | 210 | | | | | 215 | - | _ | - | | 220 | - | | _ | |
| | Glu | Val | Tyr | Phe | Thr | Gly | Pro | Gly | Trp | Glu | Ala | Arg | Gly | Ser | Phe | Ser |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| | Gln | Ala | Asp | Val | His | Arg | Gln | Val | Ala | Ile | Val | Phe | Arg | Thr | Pro | Pro |
| 25 | | | | | 245 | | | | | 250 | | | | | 255 | |
| | Tyr | Ala | Asp | | Ser | Leu | Gln | Ala | | Val | Arg | Val | Ser | | Gln | Leu |
| | _ | _ | | 260 | _ | _ | | | 265 | | _ | | | 270 | | _ |
| | Arg | Arg | | Ser | Asp | Arg | Glu | | Ser | Glu | Pro | Met | | Phe | GIn | Tyr |
| 30 | T 011 | D=-0 | 275 | mb | 7 | 7 | 7 | 280 | 7 | T1. | a 1 | ~1 | 285 | 2 | T | 7 ~~ |
| 30 | Leu | 290 | Азр | 1111 | мэр | Asp | 295 | urs | ALG | 116 | GIU | Glu 300 | цув | Arg | цуъ | Arg |
| | Thr | | Glu | Thr | Phe | Lvs | | Tle | Met | Lvs | Lvs | Ser | Pro | Phe | Ser | Glv |
| | 305 | - / - | 014 | | | 310 | | 110 | | _,, | 315 | 501 | 110 | 1 110 | | 320 |
| | | Thr | Asp | Pro | Arq | | Pro | Pro | Arq | Arq | | Ala | Val | Pro | Ser | |
| 35 | | | - | | 325 | | | | _ | 330 | | | | | 335 | _ |
| | Ser | Ser | Ala | Ser | Val | Pro | Lys | Pro | Ala | Pro | Gln | Pro | Tyr | Pro | Phe | Thr |
| | | | | 340 | | | | | 345 | | | | | 350 | | |
| | Ser | Ser | Leu | Ser | Thr | Ile | Asn | Tyr | Asp | Glu | Phe | Pro | Thr | Met | Val | Phe |
| | | | 355 | | | | | 360 | | | | | 365 | | | |
| 40 | Pro | | Gly | Gln | Ile | Ser | | Ala | Ser | Ala | Leu | Ala | Pro | Ala | Pro | Pro |
| | | 370 | _ | _ | | _ • | 375 | | _ | | | 380 | | | | |
| | | Val | Leu | Pro | Gln | | Pro | Ala | Pro | Ala | | Ala | Pro | Ala | Met | |
| | 385 | | . | | ~1 | 390 | | | | | 395 | | - | | D | 400 |
| 45 | ser | Ата | геп | АТа | | Ата | Pro | Ата | Pro | | Pro | Val | Leu | | | GIY |
| 43 | Dro | Dro | Cln | ח ה | 405 | . ה ה | Dro | Dro | ח ז ה | 410 | T | Pro | The | | 415 | Gl ₁ |
| | FIO | FIU | GIII | 420 | Val | AIG | FIU | FIU | 425 | PIO | цуз | PIO | 1111 | 430 | ліа | GIY |
| | Glu | Glv | Thr | | Ser | Glu | Ala | Leu | | Gln | Leu | Gln | Phe | | Asp | Glu |
| | | 1 | 435 | | | | | 440 | | | | | 445 | 110 P | | |
| 50 | qaA | Leu | | Ala | Leu | Leu | Gly | | Ser | Thr | Asp | Pro | | Val | Phe | Thr |
| | • | 450 | • | | | | 455 | | | | | 460 | | | | |
| | Asp | | Ala | Ser | Val | Asp | | Ser | Glu | Phe | Gln | Gln | Leu | Leu | Asn | Gln |
| | 465 | | | | | 470 | | | | | 475 | | | | | 480 |
| | Gly | Ile | Pro | Val | | Pro | His | Thr | Thr | | Pro | Met | Leu | Met | Glu | Tyr |
| 55 | | | | | 485 | | | | | 490 | | | | | 495 | |
| | Pro | Glu | Ala | Ile | Thr | Arg | Leu | Val | Thr | Gly | Ala | Gln | Arg | Pro | Pro | Asp |

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500
                                       505
       Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
                                  520
       Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
  5
                              535
                                                  540
       Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
                           550
                                            555
       Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
                      565
                                          570
       Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
 10
                   580
                                     585
       Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
                                   600
                                                     605
       Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
 15
                              615
       Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
                   630
                                             635
       Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
                                      650
      Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
 20
                                      665
      Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
             675
                                  680
      Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr
25
                            695
      Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
                       710
                                             715
      Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                     725
                                          730
      Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
30
                  740
                                     745
      Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
                                760
                                                    765
      Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
35
                              775
                                                780
      Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
                          790
               (2) INFORMATION FOR SEQ ID NO:142:
40
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2394 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
45
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: CDNA
            (ix) FEATURE:
50
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
55
     ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
```

| | | | | | | | | | | 295 | | | | | | | |
|----|----------|-----|-----|-----|-------------------|-----|-----|-----|-----|-----------|-----|-----|-----|-----|-----------|-----|-----|
| | Met 1 | Val | Ser | Lys | Gly 5 | Glu | Glu | Leu | Phe | Thr 10 | Gly | Val | Val | Pro | Ile 15 | Leu | |
| 5 | | | | | GGC Gly | | | | | | | | | | | | 96 |
| 10 | | | | | GAT Asp | - | | | _ | | | | | | | _ | 144 |
| 15 | | | | _ | AAG Lys | | | _ | | | | | | _ | _ | | 192 |
| | | | | | GTG Val | | | | | | | | | | | | 240 |
| 20 | | | | | TTC Phe 85 | | | | | | | | | | | | 288 |
| 25 | | | | | TTC Phe | | | | | | | | | | | | 336 |
| 30 | | | | | GGC Gly | | | | | | | | | | | _ | 384 |
| 35 | | | | | GAG Glu | | | | | | | | | | _ | | 432 |
| 55 | | | | | CAC His | | | | | | | | | _ | | | 480 |
| 40 | | | | | AAC Asn 165 | | | | | | | | | | | | 528 |
| 45 | | | | | GAC Asp | | | | | | | | | | | | 576 |
| 50 | | | | | CCC Pro | | | | | | | | | | | | 624 |
| 55 | | | | | AAC Asn | | | | | | | | | | | | 672 |
| 55 | GTG | ACC | GCC | GCC | GGG | ATC | ACT | CTC | GGC | ATG | GAC | GAG | CTG | TAC | AAG | TCC | 720 |

| | | | | | | | | | | 296 | | | | | | | |
|----|-------------------|-------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|-------------------|--------------------|
| | Va: 22: | l Thi | r Ala | Ala | a Gly | / Ile 230 | Thr | Lev | Gly | / Met | 235 | | ı Leı | ту: | r Ly | s Ser 240 | |
| 5 | GG? Gl | A CTC | AGA Arg | TCT Ser | CGA Arg 245 | , Ala | : ATG | GAC Asp | GAA Glu | Leu 250 | Phe | C CCC | C CTO | C ATO | 2 TTC Phe 255 | C CCG Pro | 768 |
| 10 | GC# Ala | A GAG | CCA Pro | GCC Ala 260 | Gln | GCC Ala | : TCT Ser | Gly | Pro 265 | Туг | GTC Val | GAC Glu | ATC | 270 270 | e Glu | G CAG | 816 |
| 15 | CCC Pro | AAG Lys | CAG Gln 275 | CGG Arg | GGC Gly | ATG Met | CGC | TTC Phe 280 | CGC Arg | TAC | AAG Lys | TGC Cys | GAG Glu 285 | Gly | G CGC | TCC Ser | 864 |
| | GCG Ala | GGC Gly 290 | AGC Ser | ATC Ile | CCA Pro | GGC Gly | GAG Glu 295 | AGG Arg | AGC Ser | ACA Thr | GAT Asp | ACC Thr | Thr | Lys | ACC Thr | CAC His | 912 |
| 20 | CCC Pro 305 | Thr | ATC Ile | AAG Lys | ATC Ile | AAT Asn 310 | GGC Gly | TAC Tyr | ACA Thr | GGA Gly | CCA Pro 315 | GGG Gly | ACA Thr | GTG Val | CGC | ATC Ile 320 | 960 |
| 25 | TCC Ser | CTG Leu | GTC Val | ACC Thr | AAG Lys 325 | GAC Asp | CCT Pro | CCT Pro | CAC His | CGG Arg 330 | CCT Pro | CAC His | CCC Pro | CAC His | GAG Glu 335 | CTT | 1008 |
| 30 | GTA Val | GGA Gly | AAG Lys | GAC Asp 340 | TGC Cys | CGG Arg | GAT Asp | GGC Gly | TTC Phe 345 | TAT Tyr | GAG Glu | GCT Ala | GAG Glu | CTC Leu 350 | TGC Cys | CCG Pro | 1056 |
| 35 | GAC Asp | CGC Arg | TGC Cys 355 | ATC Ile | CAC His | AGT Ser | TTC Phe | CAG Gln 360 | AAC Asn | CTG Leu | GGA Gly | ATC Ile | CAG Gln 365 | TGT Cys | GTG Val | AAG Lys | 1104 |
| | AAG Lys | CGG Arg 370 | GAC Asp | CTG Leu | GAG Glu | CAG Gln | GCT Ala 375 | ATC Ile | AGT Ser | CAG Gln | CGC Arg | ATC Ile 380 | CAG Gln | ACC Thr | AAC Asn | AAC Asn | 1152 |
| 40 | AAC Asn 385 | CCC Pro | TTC Phe | CAA Gln | GTT Val | CCT Pro 390 | ATA Ile | GAA Glu | GAG Glu | CAG Gln | CGT Arg 395 | GGG Gly | GAC Asp | TAC Tyr | GAC Asp | CTG Leu 400 | 1200 |
| 45 | AAT Asn | GCT Ala | GTG Val | Arg | CTC Leu 405 | TGC Cys | TTC Phe | CAG Gln | Val | ACA Thr 410 | GTG Val | CGG Arg | GAC Asp | CCA Pro | TCA Ser 415 | GGC Gly | 1248 |
| 50 | AGG Arg | CCC Pro | CTC Leu | CGC Arg 420 | CTG Leu | CCG Pro | CCT Pro | Val | CTT Leu 425 | CCT Pro | CAT His | CCC Pro | ATC Ile | TTT Phe 430 | GAC Asp | AAT Asn | 1296 |
| 55 | CGT Arg | Ата | CCC / Pro / 435 | AAC Asn | ACT Thr | GCC Ala | Glu | CTC Leu 440 | AAG . Lys | ATC Ile | TGC Cys | Arg | GTG Val 445 | AAC Asn | CGA Arg | AAC Asn | 1344 |
| | TCT | GGC : | AGC ' | rgc · | CTC (| GGT (| GGG (| GAT (| GAG . | ATC | TTC | CTA | CTG | TGT | GAC | AAG | 1392 296 |

| | | | | | | | | | | 297 | | | | | • | | |
|-----|-----|-------------------|-----|-----|-----|-----|-------------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|------|
| | Ser | Gly 450 | Ser | Cys | Leu | Gly | Gly 455 | Asp | Glu | Ile | Phe | Leu 460 | Leu | Cys | Asp | Lys | |
| 5 | | CAG Gln | | | | | | | | | | | | | | | 1440 |
| 10 | | CGA Arg | | | | | | | | | | | | | | | 1488 |
| 15 | | TTC Phe | | | | | | | | | | | | | | | 1536 |
| ,,, | | GTC Val | | | | | | | | | | | | | | | 1584 |
| 20 | | ATG Met 530 | | | | | | | | | | | | | | | 1632 |
| 25 | | GAG Glu | | | | | | | | | | | | | | | 1680 |
| 30 | | AGT Ser | | | | | | | | | | | | | | | 1728 |
| 25 | | GCT Ala | | | | | | | | | | | | | | | 1776 |
| 35 | | CCC Pro | | | | | | | | | | | | | | | 1824 |
| 40 | | CCC Pro 610 | | | | | | | | | | | | | | | 1872 |
| 45 | | GCC Ala | | | | | | | | | | | | | | | 1920 |
| 50 | | GCT Ala | | | | | | | | | | | | | | | 1968 |
| 55 | | GTC Val | | | | | | | | | | | | | | | 2016 |
| 55 | AAG | CCC | ACC | CAG | GCT | GGG | GAA | GGA | ACG | CTG | TCA | GAG | GCC | CTG | CTG | CAG | 2064 |

| • | | | | | | | | | | 298 | | | | | | | |
|----|-------------------|-------------------|-------------------|-------------------|-------------------|-----------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| | Lys | Pro | Thr 675 | Gln | Ala | Gly | Glu | Gly 680 | | Leu | Ser | Glu | Ala 685 | Leu | Leu | Gln | |
| 5 | CTG Leu | CAG Gln 690 | TTT Phe | GAT Asp | GAT Asp | GAA Glu | GAC Asp 695 | Leu | GGG Gly | GCC Ala | TTG Leu | CTT Leu 700 | GGC Gly | AAC Asn | AGC Ser | ACA Thr | 2112 |
| 10 | GAC Asp 705 | CCA Pro | GCT Ala | GTG Val | TTC Phe | ACA Thr 710 | GAC Asp | CTG Leu | GCA Ala | TCC | GTC Val 715 | GAC Asp | AAC Asn | TCC Ser | GAG Glu | TTT Phe 720 | 2160 |
| 15 | CAG Gln | CAG Gln | CTG Leu | CTG Leu | AAC Asn 725 | CAG Gln | GGC Gly | ATA Ile | CCT Pro | GTG Val 730 | GCC Ala | CCC Pro | CAC His | ACA Thr | ACT Thr 735 | GAG Glu | 2208 |
| | CCC Pro | ATG Met | CTG Leu | ATG Met 740 | GAG Glu | TAC Tyr | CCT Pro | GAG Glu | GCT Ala 745 | ATA Ile | ACT Thr | CGC Arg | CTA Leu | GTG Val 750 | ACA Thr | GGG Gly | 2256 |
| 20 | GCC Ala | CAG Gln | AGG Arg 755 | CCC Pro | CCC Pro | GAC Asp | CCA Pro | GCT Ala 760 | CCT Pro | GCT Ala | CCA Pro | CTG Leu | GGG Gly 765 | GCC Ala | CCG Pro | GGG Gly | 2304 |
| 25 | CTC Leu | CCC Pro 770 | AAT Asn | GGC Gly | CTC Leu | CTT Leu | TCA Ser 775 | GGA Gly | GAT Asp | GAA Glu | GAC Asp | TTC Phe 780 | TCC Ser | TCC Ser | ATT Ile | GCG Ala | 2352 |
| 30 | GAC Asp 785 | ATG Met | GAC Asp | TTC Phe | TCA Ser | GCC Ala 790 | CTG Leu | CTG Lėu | AGT Ser | CAG Gln | ATC Ile 795 | AGC Ser | TCC Ser | TAA | | | 2394 |
| | | | (2) | INI | FORMA | TION | FOF | R SE | Q ID | NO:1 | L 43: | | | | | | |
| 35 | | (i | (A) (B) | LENC TYPE | TH: : am | HARA 797 nino NESS | amir acid | no ad | cids | | | | | | | | |
| 40 | | (i (v | (D) | TOPO | ULE | : li TYPE YPE: | near : pr | otei | i n | | | | | | | | |
| 45 | | (x | i) S | EQUE | NCE | DESC | RIPI | : NOI | SEC |) ID | NO:1 | 43: | | | | | |
| | 1 | Val | | | 5 | | | | | 10 | | | | | 15 | | |
| 50 | | Glu Gly | | 20 | | | | | 25 | | | | | 30 | | | |
| | | Thr | 35 | | | Leu | Pro | 40 | | | Pro | Thr | 45 | | | | |
| 55 | Leu 65 | Thr | | | | Gln 70 | | | | | Tyr 75 | | | | | A U | |
| | Gln | His . | Asp | Phe | Phe | Lys | Ser | Ala | Met | Pro | Glu | Gly | Tyr | Val | Gln | Glu | |

| | _ | _, | - 1 | ~1 | 85 | • | | | ~ 3. | 90 | _ | _ | 1 | _ | 95 | 63 |
|------|-----|-------|------------|------|-------|------|------|-----------|-------------|------|------------|-------|-------------|-------|------|-----------|
| | Arg | Thr | He | | Phe | Lys | Asp | Asp | | Asn | Tyr | Lys | Thr | Arg | Ala | Glu |
| | | | | 100 | | | | | 105 | | | | | 110 | | |
| | Val | Lys | | Glu | Gly | Asp | Thr | | Val | Asn | Arg | Ile | | Leu | Lys | Gly |
| 5 | | | 115 | | | | | 120 | | | | | 125 | | | |
| | Ile | Asp | Phe | Lys | Glu | Asp | Gly | Asn | Ile | Leu | Gly | His | Lys | Leu | Glu | Tyr |
| | | 130 | | | | | 135 | | | | | 140 | | | | |
| | Asn | Tyr | Asn | Ser | His | Asn | Val | Tyr | Ile | Met | Ala | Asp | Lys | Gln | Lys | Asn |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| 10 | Gly | Ile | Lys | Val | Asn | Phe | Lys | Ile | Arg | His | Asn | Ile | Glu | Asp | Gly | Ser |
| | | | | | 165 | | | | | 170 | | | | | 175 | |
| | Val | Gln | Leu | Ala | Asp | His | Tyr | Gln | Gln | Asn | Thr | Pro | Ile | Gly | Asp | Gly |
| | | | | 180 | | | | | 185 | | | | | 190 | | |
| | Pro | Val | Leu | Leu | Pro | Asp | Asn | His | Tyr | Leu | Ser | Thr | Gln | Ser | Ala | Leu |
| 15 | | | 195 | | | | | 200 | | | | | 205 | | | |
| | Ser | Lys | Asp | Pro | Asn | Glu | Lys | Arg | Asp | His | Met | Val | Leu | Leu | Glu | Phe |
| | | 210 | | | | | 215 | | | | | 220 | | | | |
| | Val | Thr | Ala | Ala | Gly | Ile | Thr | Leu | Gly | Met | Asp | Glu | Leu | Tyr | Lys | Ser |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| 20 | Gly | Leu | Arg | Ser | | Ala | Met | qaA | Glu | Leu | Phe | Pro | Leu | Ile | Phe | Pro |
| | | | | | 245 | | | | | 250 | | | | | 255 | |
| | Ala | Glu | Pro | | Gln | Ala | Ser | Gly | Pro | Tyr | Val | Glu | Ile | Ile | Glu | Gln |
| | | | | 260 | | | | | 265 | | | | | 270 | | |
| | Pro | Lys | Gln | Arg | Gly | Met | Arg | | Arg | Tyr | Lys | Cys | Glu | Gly | Arg | Ser |
| 25 | | _ | 275 | | | | | 280 | | | | | 285 | | | |
| | Ala | | Ser | Ile | Pro | Gly | | Arg | Ser | Thr | Asp | | Thr | Lys | Thr | His |
| | | 290 | | _ | | _ | 295 | | | _ | | 300 | | | _ | |
| | | Thr | IIe | Lys | IIe | | GIY | Tyr | Thr | GIY | | GIA | Thr | Val | Arg | |
| 00 | 305 | _ | | 1 | | 310 | _ | _ | • | _ | 315 | • | _ | | ~1 | 320 |
| 30 · | Ser | Leu | Val | Thr | _ | Asp | Pro | Pro | His | _ | Pro | His | Pro | His | | Leu |
| | | ~3 | | _ | 325 | _ | | ~3 | | 330 | ~ 1 | | ~1 | | 335 | |
| | vaı | GIA | гàг | _ | Cys | Arg | Asp | GIY | | ryr | GIU | Ala | GIU | Leu | Cys | Pro |
| | 7 | 7 | ~ - | 340 | 71: - | | Db.s | G3 | 345 | 7 | a 1 | T1. | a 1- | 350 | 171 | ¥ |
| 35 | Asp | Arg | 355 | 116 | urs | 261 | PHE | 360 | ASII | Leu | GIŸ | 116 | 365 | Cys | val | Lys |
| 33 | Lve | 7 ~ ~ | | Lou | Cl. | Cln | λ1- | | Co.~ | Cln | 7 ~~ | Tlo | | Thr | λan | Acn |
| | цуь | 370 | wab | neu | Giu | GIII | 375 | 116 | 261 | GIII | Arg | 380 | GIII | 1111 | ASII | ASII |
| | λen | | Dhe | Gln | Val | Pro | | Glu | Glu | Gln | λνα | | λευ | Tyr | Nen | T.eu |
| | 385 | 110 | 1110 | 0111 | • | 390 | 110 | Olu | OIU | OIII | 395 | Cry | ASP | - 7 - | тор | 400 |
| 40 | | Δla | Val | Ara | Len | | Phe | Gln | Val | Thr | | Δνα | Δsn | Pro | Ser | |
| , 0 | | | *** | | 405 | O, D | | 0111 | •42 | 410 | V U I | ***** | nop. | | 415 | 017 |
| | Ara | Pro | Leu | Ara | | Pro | Pro | Val | Leu | | His | Pro | Ile | Phe | | Asn |
| | 3 | | | 420 | | | | | 425 | | | | | 430 | | |
| | Arq | Ala | Pro | Asn | Thr | Ala | Glu | Leu | | Ile | Cvs | Ara | Val | Asn | Arq | Asn |
| 45 | _ | | 435 | | | | | 440 | -,- | | -3 | | 445 | | | |
| | Ser | Gly | Ser | Cys | Leu | Gly | Gly | Asp | Glu | Ile | Phe | Leu | Leu | Cys | Asp | Lys |
| | | 450 | | • | | - | 455 | | | | | 460 | | - | | - |
| | Val | Gln | Lys | Glu | Asp | Ile | Glu | Val | Tyr | Phe | Thr | Gly | Pro | Gly | Trp | Glu |
| | 465 | | - | | - | 470 | | | - | | 475 | • | | - | - | 480 |
| 50 | Ala | Arg | Gly | Ser | Phe | Ser | Gln | Ala | Asp | Val | His | Arg | Gln | Val | Ala | Ile |
| _ | | | | | 485 | | | | | 490 | | | | | 495 | |
| | Val | Phe | Arg | Thr | Pro | Pro | Tyr | Ala | Asp | Pro | Ser | Leu | Gln | Ala | Pro | Val |
| | | | | 500 | | | | | 505 | | | | | 510 | | |
| | Arg | Val | | Met | Gln | Leu | Arg | Arg | Pro | Ser | Asp | Arg | | Leu | Ser | Glu |
| 55 | | | 515 | | | | | 520 | | | | | 525 | | | |
| | Pro | Met | Glu | Phe | Gln | Tyr | Leu | Pro | Asp | Thr | Asp | Asp | Arg | His | Arg | Ile |

| | | 530 | | | | | 535 | | | | | 540 | | | | |
|----|------------|-----|------------|-----|-----|------------|-----|-----|-----|-----|------------|-----|-----|-----|-----|-----|
| | Glu | Glu | Lys | Arg | Lys | Arg | Thr | Tyr | Glu | Thr | Phe | Lys | Ser | Ile | Met | Lvs |
| | 545 | | | | | 550 | | | | | 555 | | | | | 560 |
| 5 | | | Pro | | 565 | | | | | 570 | | | | | 575 | |
| | | | Val | 580 | | | | | 585 | | | | | 590 | | |
| | | | Tyr 595 | | | | | 600 | | | | | 605 | | | |
| 10 | | 610 | Thr | | | | 615 | | | | | 620 | | | | |
| | 625 | | Pro | | | 630 | | | | | 635 | | | | | 640 |
| 15 | | | Pro | | 645 | | | | | 650 | | | | | 655 | |
| | | | Leu | 660 | | | | | 665 | | | | | 670 | | |
| | | | Thr 675 | | | | | 680 | | | | | 685 | | | |
| 20 | | 690 | Phe | | | | 695 | | | | | 700 | | | | |
| | 705 | | Ala | | | 710 | | | | | 715 | | | | | 720 |
| 25 | | | Leu | | 725 | | | | | 730 | | | | | 735 | |
| | | | Leu | 740 | | | | | 745 | | | | | 750 | | |
| | | | Arg 755 | | | | | 760 | | | | | 765 | | | |
| 30 | | 770 | Asn | | | | 775 | | | | | 780 | | Ser | Ile | Ala |
| | Asp 785 | Met | qaA | Phe | Ser | Ala 790 | Leu | Leu | Ser | Gln | Ile 795 | Ser | Ser | | | |

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CLAIMS

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
- 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

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chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on an
 intracellular pathway is to be determined.
 - 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
 - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 25 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

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11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.

- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore
 which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.

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- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
- 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

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17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
- 20. A method according to any of the preceding claims, wherein the light to be measured
 passes through a filter which selects the desired component of the light to be measured and rejects other components.
 - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

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- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.
- 23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
 - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
 - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
 - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

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- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.
- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
- 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step(c) comprises determining a change in the spatial distribution of the fluorescence.
 - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

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38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.

- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
 - 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
 - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

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- 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

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45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.

- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

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48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.

- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
 - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

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53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
 - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
 - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
 - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

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62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
- 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
 - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
 - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

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76. An apparatus according to claim 73 in which component f is a CCD camera.

77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

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- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
 - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in back-30 tracking of signal transduction pathways as defined herein.

- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 10 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.

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- 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

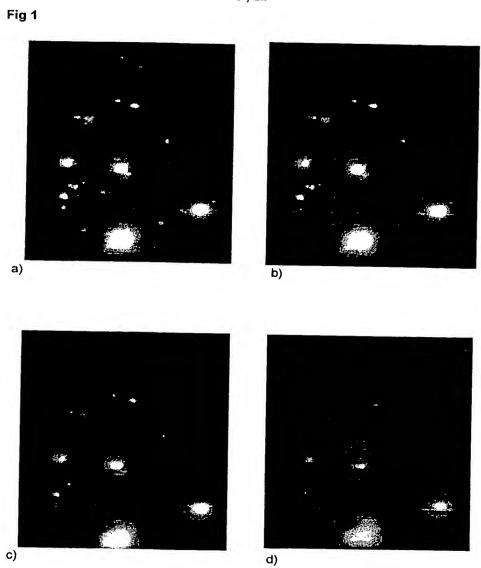


Fig 2

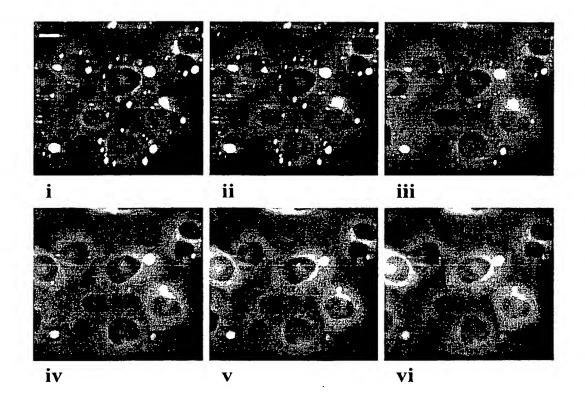
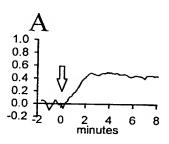
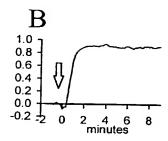
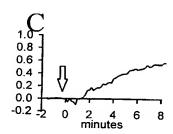
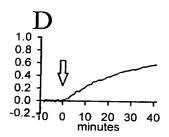


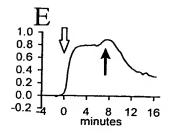
Fig 3

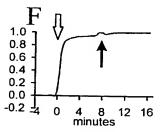


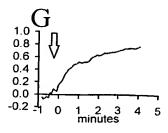


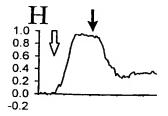






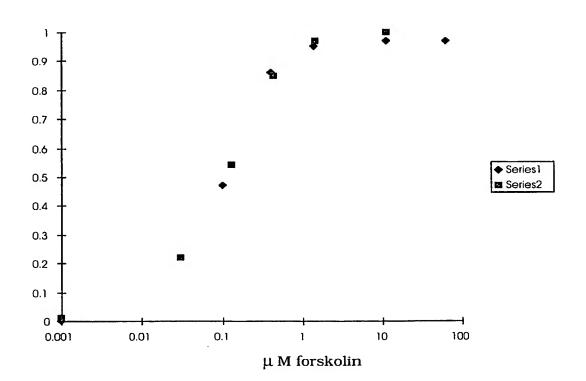






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Fig 4



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Fig 5

| [forskolin]µM | $t_{1/2\text{max}}/s$ | t _{max} /s |
|---------------|-----------------------|---------------------|
| 1 | 115±21 | 310±31 |
| 10 | 69±14 | 224±47 |
| 50 | 47±10 | 125±28 |

Fig 6

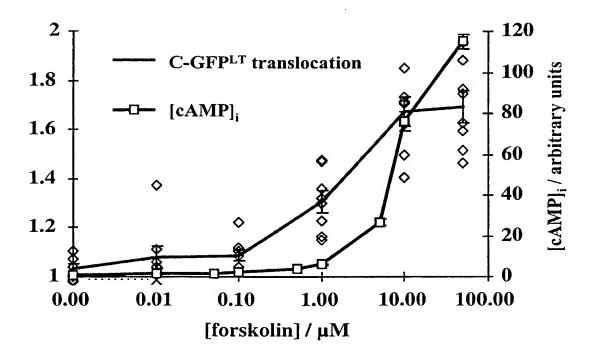
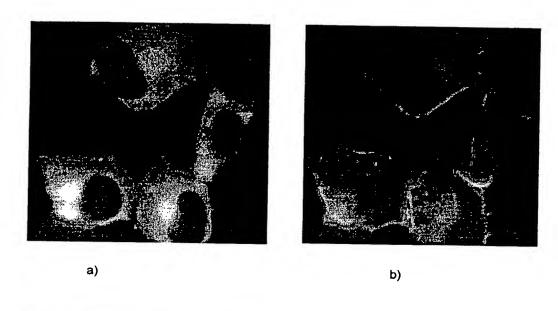


Fig 7



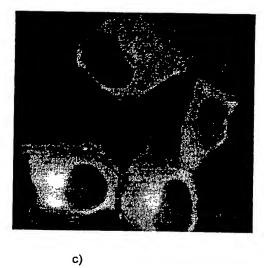
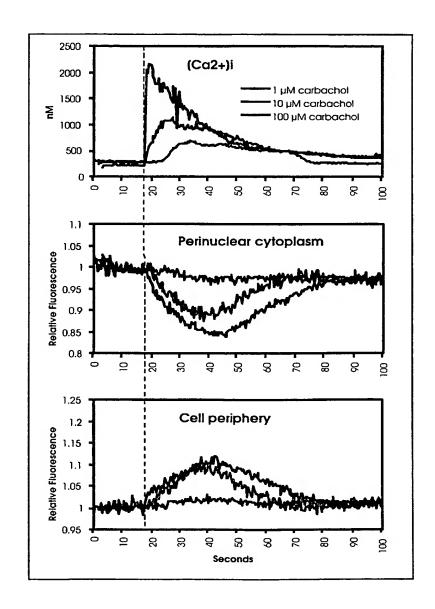
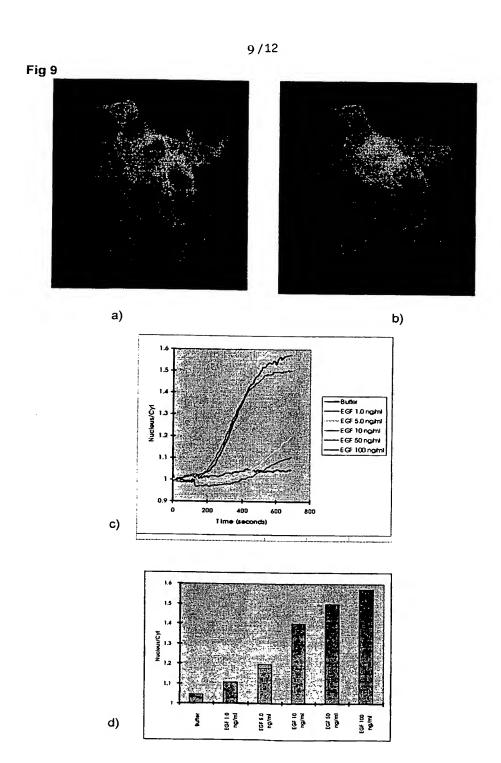


Fig 8

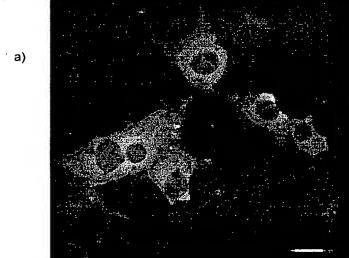


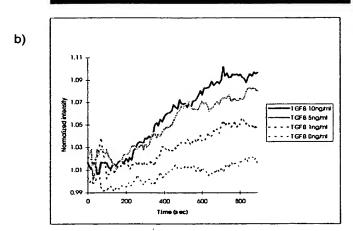


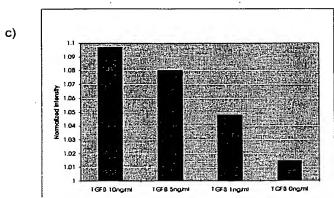
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Fig 11

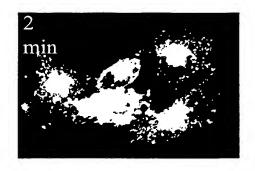


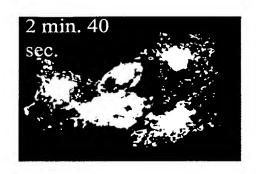
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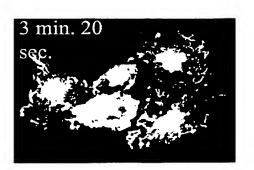
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Fig. 12













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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| (51) International Patent Classification 6: | | (11) International Publication Number: WO 98/45704 |
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| G01N 33/50, C12Q 1/48, 1/25 | A3 | (43) International Publication Date: 15 October 1998 (15.10.98) |
| (21) International Application Number: PCT/DKS (22) International Filing Date: 7 April 1998 (C) (30) Priority Data: 0392/97 7 April 1997 (07.04.97) (71) Applicant (for all designated States except US): NORDISK A/S [DK/DK]; Novo Allé, DK-2880 B. | 07.04.9 D NOV | BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NI, PT, SE), OAPI patent (BE, BI, CE, CE, CE, CE, CE, CE, CE, CE, CE, CE |
| (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): THASTRU [DK/DK]; Birkevej 37, DK-3460 Birkerød (D TERSEN BJØRN, Sara [DK/DK]; Klampenborg DK-2800 Lyngby (DK). TULLIN, Søren [DK/DK] Gjellerups Alle 18, DK-2860 Søborg (DK). K Almholt [DK/DK]; Eigilsgade 32, 4. tv, DK-2300 havn S (DK). SCUDDER, Kurt [US/DK]; Lavenc 70, DK-2830 Virum (DK). (74) Common Representative: NOVO NORDISK A/S; at Keilberg, Novo Allé, DK-2880 Bagsværd (DK). | K). PH vej 102 K]; Ka ASPER Køber delhave | Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 22 April 1999 (22.04.99) |

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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Int. tional Application No PCT/DK 98/00145

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| IPC 6 | SIFICATION OF SUBJECT MATTER G01N33/50 C12Q1/48 C12Q1/ | 25 | | | | |
| | to International Patent Classification (IPC) or to both national class | ification and IPC | | | | |
| | SEARCHED | | | | | |
| 170 6 | documentation searched (classification system followed by classific G01N C12Q C12N C07K | | | | | |
| | ation searched other than minimum documentation to the extent the | | | | | |
| | and the state of t | base and, where practical, so | ∍arch terms used) | | | |
| C. DOCUM | ENTS CONSIDERED TO BE RELEVANT | | | | | |
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| Y | see the whole document see claims | | 64-82,88 28,29, 41,61-63 | | | |
| Х | WO 91 01305 A (UNIV WALES MEDIC) 7 February 1991 | NE) | 1-27, 30-40, 42-60, 64-84, | | | |
| Υ | see page 4, line 15 - line 20 see claims see examples 1-10 | | 87,88 28,29, 41,61-63 | | | |
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tr. ational application No. PCT/DK 98/00145

| Box I | Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) | |
|-----------|---|---------------|
| This Inte | ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: | _ |
| 1. X | Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: | |
| 2. X | Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy). Claims Nos.: 85,86 | |
| | because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: | |
| | see FURTHER INFORMATION sheet PCT/ISA/210 | |
| 3. | Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). | |
| Box II | Observations where unity of invention is lacking (Continuation of item 2 of first sheet) | ┨ |
| | rnational Searching Authority found multiple inventions in this international application, as follows: | $\frac{1}{2}$ |
| | ectioning Additionly loand maniple inventions in this international application, as follows: | ĺ |
| | see additional sheet | |
| | | I |
| 1. X | As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims. | |
| 2 | As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. | |
| 3 | As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: | |
| 4. | No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: | |
| Remark o | The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees. | |

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 85,86

The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

 Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

International Application No. PCT/DK 98/00145

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network



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